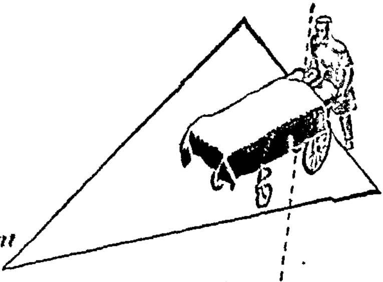

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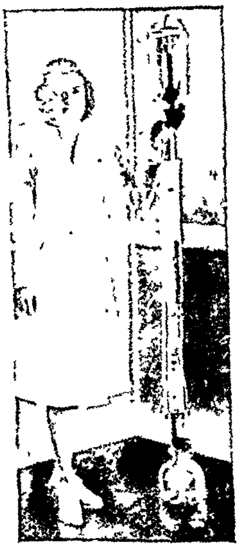

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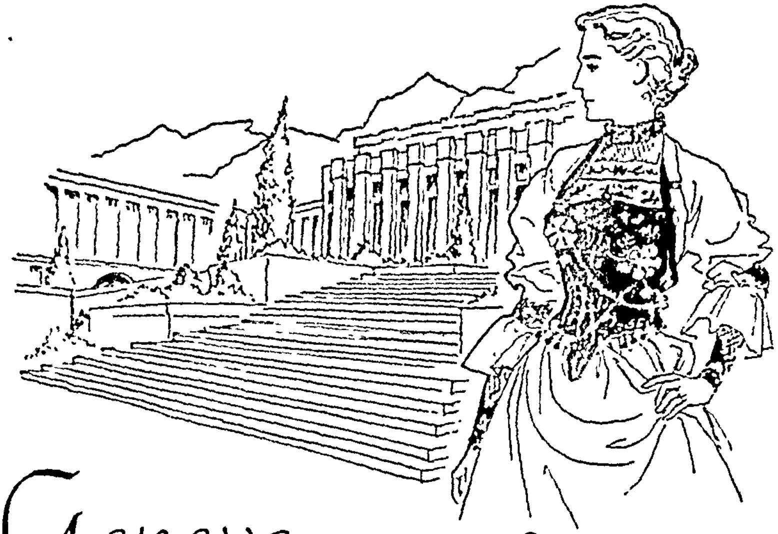

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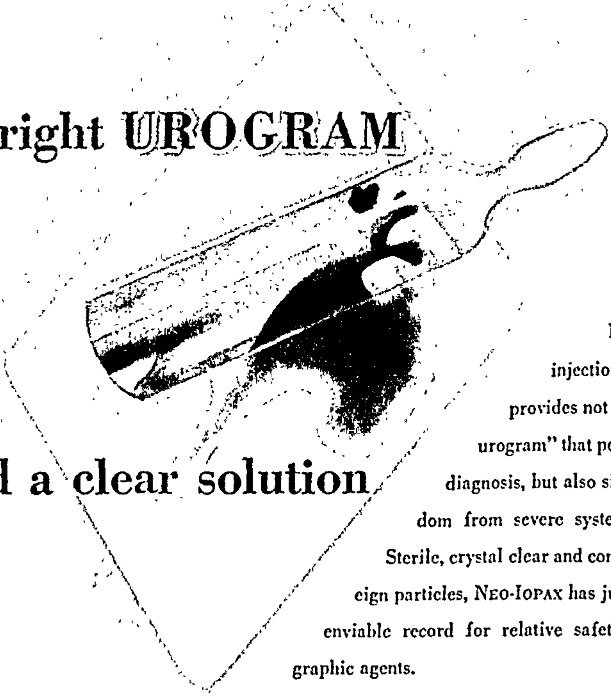

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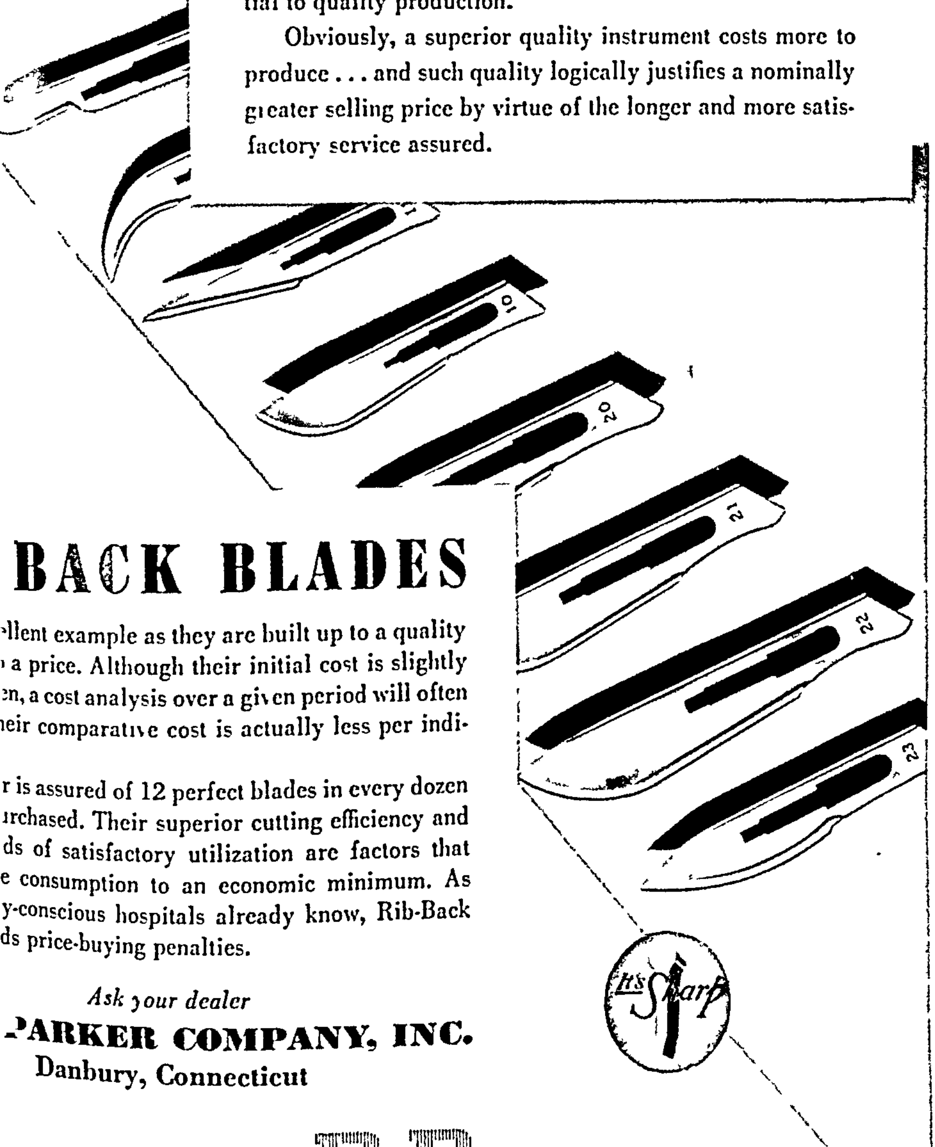

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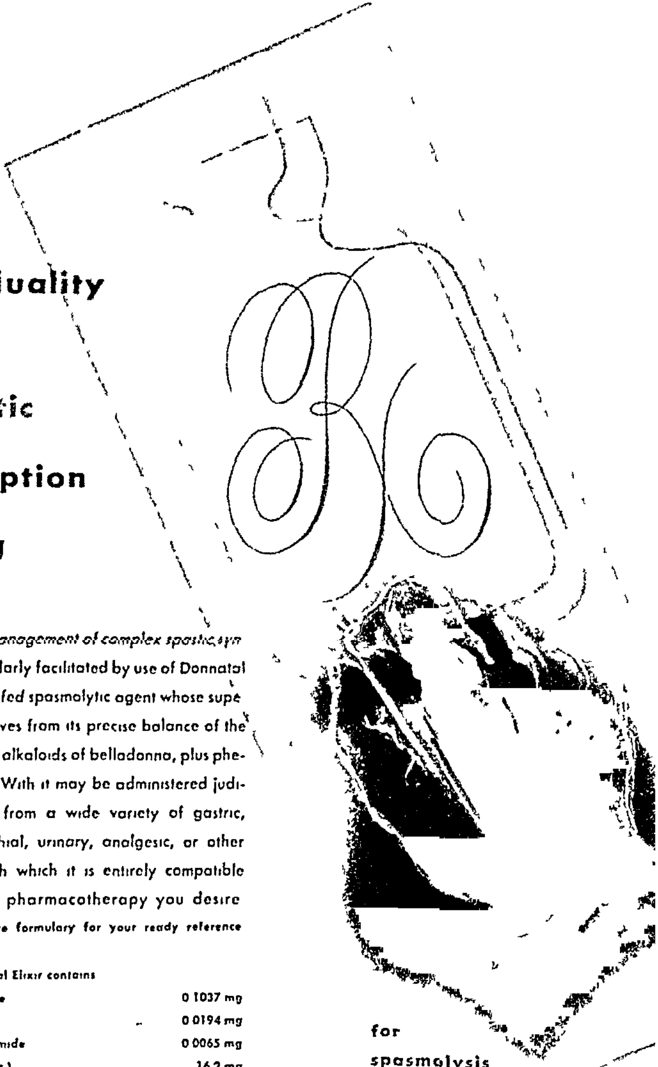

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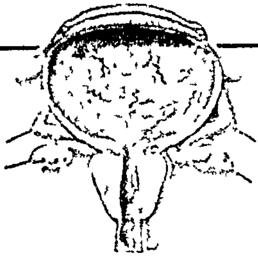

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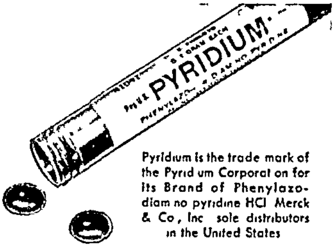

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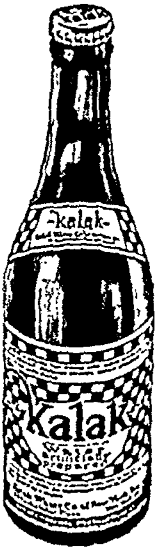

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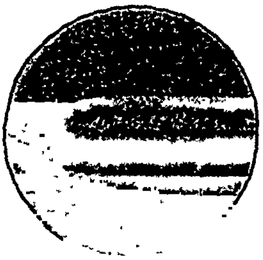

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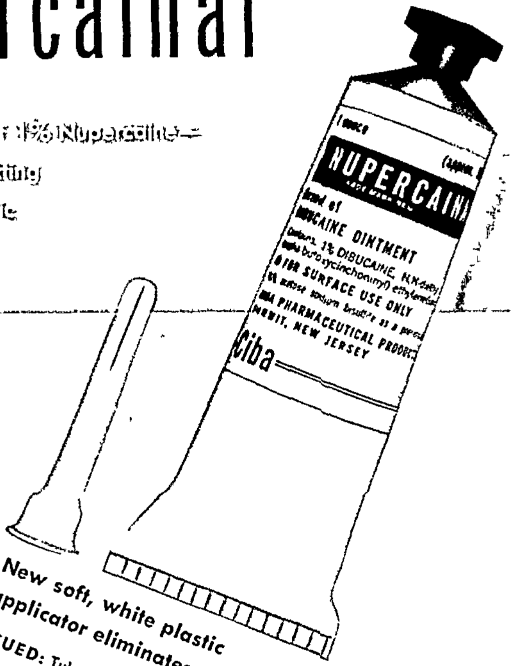

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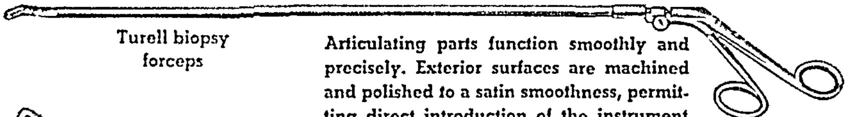

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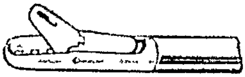

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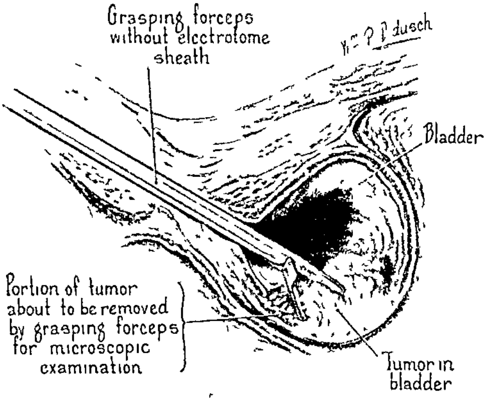

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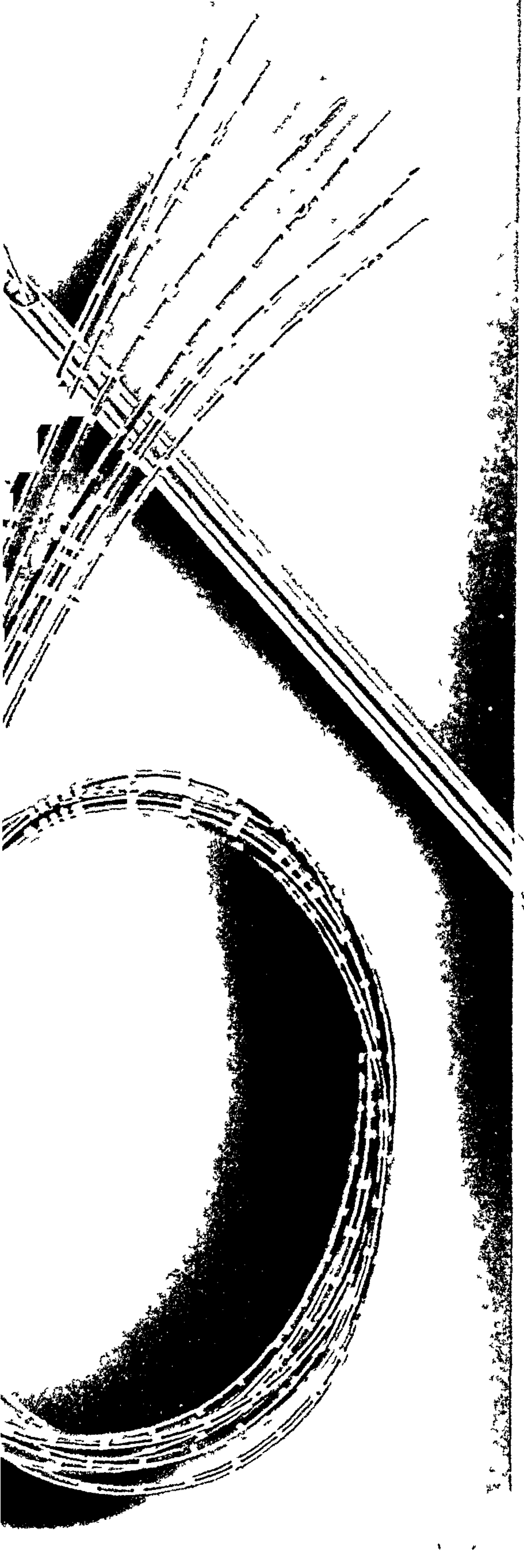

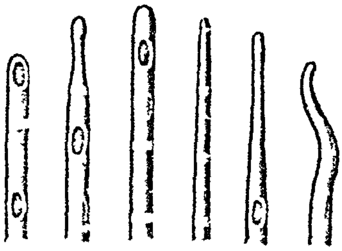

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ETIOLOGY AND MANAGEMENT OF RENAL LITHIASIS[1]

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The investigation of the etiologic factors associated with the formation of renal calculi has been stressed with increasing frequency by urologic surgeons in recent years.

In view of the high incidence of recurrent calculus formation in the past, it is appreciated that the surgical removal of the calculus is but one phase in the management of the patient with renal lithiasis.

Unless the causative factor or factors are ascertained in each patient and corrected, a high incidence of recurrent calculi will ensue.

An extensive preoperative investigation is essential to determine the etiologic factors in each case. This will permit their correction or eradication prior to operation, during the operative procedure or in the period of postoperative observation. Only by such study and corrective steps can the morbidity of this disease be lowered. It is generally agreed that no single etiologic factor is the causative agent in the formation of all renal calculi.

During the period of preoperative study we believe the following contributing factors merit investigation.

VITAMIN A DEFICIENCY

Clinical and experimental observations have demonstrated the relationship between stone formation and the absence or deficiency of certain essentials in the diet. "Stone areas", geographic regions in which urinary calculi are unusually prevalent, have been reported in many countries, namely India, China, Russia, Siam, England and France. From an analysis of the diet peculiar to these localities it is evident that the inhabitants subsist on fare which is deficient in certain essentials or poorly balanced in acid and alkaline ash foods. Several authors have emphasized the deficiency of vitamin A in the diet of the people in these regions.

In the experimental laboratory I have been able to produce stones similar in their chemical constituents to those observed in patients, by maintaining the animal on a diet deficient in vitamin A for an extended period of time and varying the constituents of the diet.

The following types of renal calculi have been produced:[2]

1) Stones composed of phosphates with traces of carbonates in the white rat.
2) Stones composed of carbonates with traces of phosphates in the white rat.
3) Oxalate calculi in rabbits.
4) Uric acid calculi in the Dalmatian dog.
5) Stones composed of the acetyl salts of sulfonamides in the rabbit.

Clinically, a cystine calculus in the kidney of a boy was dissolved by the use of the alkaline ash diet, a new calculus was formed by placing him on a vitamin A deficiency, high purine diet, and the newly formed stone underwent dissolution when the alkaline ash diet was resumed.

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[1] Read at annual meeting, Northeastern Section, American Urological Association, Seigniory Club, Province of Quebec, Canada, October 14, 1948.

[2] Higgins, C. C.: Renal Lithiasis. Springfield, Ill.: Charles C. Thomas, 1943.

Long and Pyrah[3] stated that 40 per cent of their patients showed subnormal dark adaptation.

Erickson and Feldman[4] observed that of 25 patients with urolithiasis, 24 had disturbed dark adaptation which varied from a mild to severe degree. In a previously reported series we noted that 48 per cent had subnormal dark adaptation. Studies for vitamin A deficiency should be made in cases such as these.

In 1934 Barney and Mintz[5] reported a series of cases in which the diagnosis of hyperparathyroidism had been substantiated by surgical intervention. In 11 or 61.1 per cent of cases, calculi were observed in the urinary tract. They concluded that hyperparathyroidism is responsible for from 4 to 5 per cent of the cases of renal lithiasis. In approximately 70 per cent of the cases of hyperparathyroidism, stones may be present, and in about 38 per cent the patient may have demonstrable pathologic changes in the bones and urinary tract.

Braasch[6] found that hyperparathyroidism was the etiologic factor in less than 0.2 per cent of the cases at the Mayo Clinic.

Sangree,[7] in a review of 50 consecutive cases of renal and ureteral calculi, observed 1 patient with a parathyroid tumor. In a previous series I reported that hyperparathyroidism was confirmed by operation in 0.6 per cent of our patients with renal calculi. Although the evidence cited by Barney and Mintz is higher than we have observed, I am of the opinion that the actual incidence of hyperparathyroidism is higher than urologists have presumed in the past. An intensive study should be made in all patients with renal lithiasis to rule out the possibility of hyperparathyroidism as a causative factor. The level of serum calcium and serum phosphorus in the blood should always be determined. If there is an elevation of the serum calcium and a lowering of the serum phosphorus additional studies of calcium balance are indicated. A *Sulkowitch* test detects the gross presence or absence of hypercalcinuria, while roentgenologic survey may reveal bone lesions compatible with the diagnosis of hyperparathyrodism. If such a diagnosis is established, exploration of the parathyroid glands is advisable for the removal of a tumor, which is usually an adenoma.

CALCIUM EXCRETION IN THE URINE

A study of the excretion of calcium in the urine should be a routine procedure. Various factors may influence the excretion of calcium. First, varying the ingestion of calcium and phosphorus, second, varying the intake of vitamin D, and third, varying the acidity of the acid ash in the diet. On a normal diet approximately 200 mg. of calcium is excreted in the urine daily.

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[3] Long, H. AND Pyrah, L. N.: Role of vitamin A deficiency in etiology of renal calculus. Brit. J. Urol., 11: 216–232, 1939.

[4] Ezickson, W. J. AND Feldman, J. B.: Signs of vitamin A deficiency in eye correlated with urinary lithiasis; report of clinical studies and investigation of 25 patients. J. A. M. A., 109: 1706–1710, 1937.

[5] Barney, J. D. AND Mintz, E. R.: Some newer conceptions of urinary stone formation. J.A.M.A., 103: 741–743, 1934.

[6] Braasch, W. F. AND Foulds, G. S.: Postoperative results of nephrolithiasis. J. Urol., 11: 525–537, 1924.

[7] Sangree, H. K.: Management and prevention of renal and ureteral calculi. J. Urol., 59: 842–845, 1948.

The excretion, when the diet is low in calcium and phosphorus and the ash is neutral, varies between 95 to 145 mg. When, however, the intake of calcium and phosphorus in increased, the excretion of calcium may attain 300 mg. daily.

Flocks[8] has observed that many patients who have, or have had, urinary calculi may show a high urinary calcium excretion while the blood calcium and phosphorus levels are normal. The exact cause of this increased excretion of calcium is obscure. In Flocks' series these comprise 60 per cent of patients with calcium stones. Thirty-five to 50 per cent show a normal or low urinary calcium.

Riegel, Royster, Gislason and Hughes[9] in a study of 15 patients with urolithiasis observed that 14 (93 per cent) had a definite increase in the renal excretion of calcium. Hyperparathyroidism had been excluded in the 15 patients. Of the 14 cases with an increased excretion of calcium in the urine, 7 (50 per cent) had impairment of renal function, while the remaining 7 patients had normal renal function.

We have previously cited the presence of hypercalcinuria in some patients with renal lithiasis, especially in the presence of impaired renal function, and stressed that hypercalcinuria per se is not a reliable sign of hyperparathyroidism. It is well known that the acid ash diet increases in certain individuals the excretion of urinary calcium and also increases the solubility of the calcium salts being excreted in the urine. In normal individuals with a wide variation in the diet, the quantitative excretion of calcium in the urine is relatively small.

INFECTION

The relationship between urinary tract infections and calculus formation is evident from a review of our clinical cases. In 100 cases of recurrent renal calculi, previously reported, infection was present in 54 of 72 patients with recurrent unilateral stones, and the culture was sterile in 18.

In this series the number of patients in whom the culture of the urine was sterile is relatively high. In several cases recurrent stones were very small. Urinary antiseptics had been administered in 9 instances. In the group of 28 patients with bilateral recurrence, infection was present in the kidneys in 23 cases and the culture of the urine was sterile in 5. The staphylococcus in pure or mixed cultures was the predominating organism, and the Proteus organisms occurred second in frequency.

In 1932 Bugbee[10] demonstrated the relationship between pre-existing pyelonephritis and the formation of renal calculi. A definite history was elicited in 23 of 29 patients with kidney stones. In 17 patients treatment had been administered during initial attack, while in the remaining 6 cases other physicians had treated the infection. At the time the patient was first observed with pyelonephritis roentgenograms revealed no calculi, but stones subsequently developed in all instances.

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[8] Flocks, R. H.: Prophylaxis and medical management of calcium urolithiasis. J. Urol., 44: 183–190, 1940.

[9] Riegel, C., Royster, H. P., Gislason, G. J. AND Hughes, P. B.: J. Urol., 57: 192–195, 1947.

[10] Bugbee, H. G.: Recurring pyelonephritis as etiological factor in nephrolithiasis. Tr. Am. A. Genito-Urin. Surg., 25: 121–131, 1932.

Harrington,[11] in a clinical study of 480 cases of urinary lithiasis, stated that at least 26 per cent of all cases which included renal, ureteral and bladder stones no infection could be demonstrated. He concluded: "The true percentage of sterile cases in this series is undoubtedly higher than 26 per cent, indicating that infection can not be indicted as the etiological agent in the majority of cases of urinary lithiasis."

In 1936 Lett,[12] in a review of 419 cases of renal lithiasis, stated the urine was sterile in 49 cases.

Brown and Earlam[13] have stated that 18 per cent of the bacilli which infect the urinary tract and 40 per cent of the strains of Staphylococcus albus have the property of splitting urea.

Complete bacteriologic studies are essential. These include a gram stain of the urinary sediment and routine culture on glucose-brain broth. In each case it should be determined if the organism possesses the power of splitting urea. Only by such study can the correct chemotherapeutic agent be employed.

FOCAL INFECTION

In 1921 Rosenow and Meisser[14] demonstrated the specificity of the streptococcus to produce urinary calculi. They inoculated the pulp of the teeth of 6 dogs with streptococci isolated from the urine of patients with calculus disease. Following this calculi developed in the dogs, and the streptococci were isolated from the urine. In view of this work I believe foci infection should be eradicated during the period of postoperative observation.

STASIS

In certain instances, stasis is definitely associated with the formation of renal calculi. Stasis is conducive to shifting the *p*H of the urine to the alkaline side and produces a fertile field for bacterial growth. Stasis may be demonstrated by intravenous urograms made prior to operation, thus forewarning the surgeon to remove or correct the causative factor at the time of surgical intervention. Likewise, similar studies should be made before the patient is dismissed from the hospital to determine whether or not stasis has been eliminated.

METABOLIC DISEASES

Gout is a metabolic disease in which excessive amounts of crystalloids may be present in the urine. The patient may form a renal calculus or experience frequent episodes of colic due to the passage of small stones or showers of uric acid crystals. Other clinical manifestations of gout, as painful joints, need not be associated with the formation of uric acid calculi. Routinely a microscope examination of the urinary sediment for uric acid crystals and urates is advisable. Normally 0.3 gm. to 1.2 gm. of uric acid is excreted daily, the amount being influenced by the diet. A blood uric acid determination is made in each case. Such information is essential if dietary management is instituted during the period of postoperative observation.

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[11] Harrington, H. L.: Clinical study of 480 cases of urinary lithiasis. J. Urol., 44: 507–519, 1940.

[12] Lett, H.: On urinary calculus, with special reference to stone in bladder. Brit. J. Urol., 8: 205–232, 1936.

[13] Brown, R. K. L. AND Earlam, M. S. S.: Relation of prolonged immobilization and urinary tract infection to renal calculus formations. Australian and New Zealand J. Surg., 3: 157–171, 1933.

[14] Rosenow, E. C. AND Meisser, J. G.: Nephritis and urinary calculi after production of chronic foci of infection. J. A. M. A., 78: 266–267, 1922.

CYSTINURIA

Cystinuria is a familial disease caused by derangement of intermediate protein metabolism. Normally, cystine is oxidized completely and the sulfur is excreted as sulfate. It has been stated that 2.5 per cent of patients with cystinuria develop calculi. We have observed 9 patients with renal calculi composed of cystine. In 1925 Seeger and Kearns[15] collected 181 cases of cystinuria, 124 of which were complicated by calculus disease.

The cystine may be found in the urine partly in solution and also in crystalline deposit. Microscopic study of the urine for cystine crystals is essential. Accurate diagnosis is of especial importance in cystine calculi, as they are quite amenable to dissolution by utilizing the alkaline ash diet.

OXALURIA

Approximately 12 to 30 mg. of oxalic acid which has an exogenous and endogenous source is excreted in the urine daily.

Examination of the urine may reveal calcium oxalate crystals in the presence of oxaluria. The reaction of the urine may be either acid or alkaline. In view of the exogenous source of oxalates their precipitation may be minimized by the restriction of foods with a high oxalic acid content.

XANTHINURIA

In 1934 Kretschmer[16] collected a series of 15 xanthine calculi and added an additional case. We have observed 2 patients with xanthine renal stones. Uric acid is the most important purine in the urine and 30 to 50 mg. of purine bases, xanthine, hypoxanthine, guanine and adenine are also present. Obviously precipitation of such salts in the urine can be minimized by dietary management.

PHOSPHATURIA

Three types of phosphaturia occur:

1) Temporary phosphaturia produced by an over abundance of foods with an excess alkaline ash or medication.

2) Permanent infected phosphaturia due to the presence of urea splitting organisms.

3) Permanent noninfected phosphaturia of unknown cause.

It is thus evident that an intensive preoperative investigation is necessary in order to correct or eliminate the causative factors responsible for stone formation. It also infers that no single etiologic factor is responsible for the formation of all renal calculi.

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[15] Seeger, S. J. AND Kearns, W. M.: Cystinuric lithiasis. J. A. M. A., 85: 4-7, 1925.

[16] Kretschmer, H. L.: Xanthin calculi; report of a case and review of literature. J. Urol., 38: 183-193, 1937.

A few remarks concerning the surgical management of patients with renal calculi is advisable. In view of the morbidity of this disease and the high incidence of recurrence or formation of a stone in the opposite kidney reported by some authors, conservative renal surgery is advisable.

In past years nephrectomy was advocated frequently for patients in whom today a more extensive nephrotomy would be performed. This is not to be criticized or condemned, since the newer urinary antiseptics were not available at that time. Infections of the urinary tract that may be readily eradicated today by our newer chemotherapeutic agents proved in the past to be resistant to the available therapy. Thus recurrent stones formed and eventually resulted in destruction of the kidney.

The majority of calculi confined to the pelvis of the kidney may be removed by pyelolithotomy. In certain instances the stone can not be extracted through a simple linear incision in the pelvis of the kidney. In such cases the pyélotomie élargie of Marion[17] or the inferior pyelolithotomy technique recommended by Zuckerkandl[18] may be employed. It is not necessary to deliver the kidney into the loin. By careful dissection the operation may be carried down to the posterior aspect of the renal pelvis and adequate exposure secured with flexible retractors. This procedure minimizes traumatizing and manhandling the kidney. Except in the presence of pronounced infection the incision in the renal pelvis is closed with 000 plain catgut. Prolonged urinary drainage is conducive to the introduction of a staphylococcus infection, regardless of meticulous care exercised in dressing the wound. The role of the staphylococcus, especially if it possesses the power of splitting urea in the formation of recurrent renal calculi, is well recognized.

Nephrolithotomy may be required and should be as conservative as possible. In 1939 we demonstrated in the experimental laboratory that immediate bleeding is less profuse and that less danger exists of infarction and atrophy of the renal parenchyma, when the incision in the parenchyma is made with a cutting current. A No. 18 catheter is inserted down into the kidney pelvis through the cortex for drainage, irrigation and removal of retained clots. Extensive nephrotomies for the removal of unilateral or bilateral stag-horn calculi can now be safely advocated.

During the last 10 years several reports recommending calycectomy have appeared in the literature. I believe this to be too radical a procedure for uncomplicated renal calculi. A heminephrectomy may be advisable in the presence of a pyocalyx associated with a stricture of the infundibulum. It may also be indicated in a kidney with two pelves in which one part of the kidney has been destroyed by infection.

Several approaches are therefore available for the removal of a calculus from the kidney. The operation accomplished by a minimal amount of trauma to the renal parenchyma is preferable.

POSTOPERATIVE MANAGEMENT

1) Maintenance of large fluid intake and output. (Distilled water for 1 year.)
2) Eradication of infection in the urinary tract.

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[17] Marion, G.: Extension of pyelotomy. J. d'urol., 13: 1–8, 1922.

[18] Zuckerkandl, O.: Ueber nierensteine. Arch. f. klin. chir., Berlin, 87: 481–489, 1908.

3) Elimination of foci infection.
4) Elimination of stasis.
5) Correction of metabolic diseases.
6) Large amounts of vitamin A.
7) Exploration of parathyroid glands if hyperparathyroidism is present.
8) Dietary management.

The dietary routine to be advised is governed by the chemical constituents of the calculus, the crystals observed in the urine and the blood chemistry findings. It is definitely influenced by the *p*H of the urine and is utilized to maintain the crystalloids responsible for the formation of the calculus in complete solution.

By maintaining the salts in complete solution, precipitation and formation of accumulations of crystalloids are prevented, thereby eliminating a requisite necessary for the formation of renal calculi. In instances in which the *p*H of the urine cannot be controlled by diet due to the presence of co-existing infection, especially the urea-splitting strains, the diet is of little value until the infection is eradicated. The mere prescribing of the diet is inadequate. The patient should be advised to check the *p*H of the urine daily and present the reports at monthly intervals. This permits adjustment of the constituents of the diet by the dietitian in order to maintain the *p*H at the desired level.

For calculi composed of phosphates and carbonates the high vitamin A acid ash diet is utilized.

In general the *p*H of the urine is maintained betwen 5.2 and 5.4 where the phosphates and carbonates are maintained in complete solution, thus keeping the urine free from crystals or sediments which precipitate in alkaline urine. We prefer to determine the *p*H of the urine in the individual patient in order to judge the point at which the salts are maintained in complete solution as some degree of individual variation occurs.

For uric acid, cystine and xanthine calculi, the high vitamin A alkaline ash diet is prescribed. The *p*H of the urine is shifted to a point where these salts are not precipitated in the urine and at the same time the alkaline salts are maintained in solution. Foods with a high purine content are also restricted for patients with uric acid calculi to minimize the amount of uric acid and urates available to be precipitated in the urine.

When the stone is composed of oxalates, foods with a high oxalic acid content are restricted. Oxalates precipitate in urine the *p*H of which may be acid or alkaline. To increase the solubility of the calcium salts the *p*H is maintained slightly on the acid side. By this routine we have reduced the incidence of recurrent renal calculi from 16.9 per cent to 4.2 per cent.

The management of a patient with renal lithiasis is a complex problem of which surgery is but one phase. Failure to give attention to etiologic factors will inevitably result in a high incidence of recurrent calculus formation. Familiarity with all phases of calculus disease, close adherence to the known concepts of stone formation, and measures to prevent recurrent lithiasis will be rewarded by a lessened incidence of calculus recurrence.

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PRIMARY RENAL ACTINOMYCOSIS[1]

EDGAR BARON AND LINO J. ARDUINO

The term primary renal actinomycosis may be misleading, inasmuch as it is bvious that the organism cannot reach the kidney without first having pene-rated the body by one of several routes. The organism may enter the body rough the mouth (causing apical abscesses of the teeth), the lung, appendix, ecum, ascending colon, or the lower urinary tract. In many respects, actinomy-osis is similar to tuberculosis in its distribution and manner in which the organ-m reaches the kidney. Just as in tuberculosis, primary renal infection is always elieved to have a portal of entry elsewhere. It is conceivable that the point of ntry of the organism may show no active lesion, or the lesion may be transient nd heal before renal involvement becomes apparent. Primary renal actinomy-osis should include those cases in which the disease is limited to the kidney, lthough the kidney may be the focus for subsequent metastatic lesions. Primary r isolated renal actinomycosis is amenable to surgical treatment and has a favor-ble prognosis, whereas generalized actinomycosis is almost uniformly fatal, with he present methods of treatment. It is usually found as a large solitary lesion, hereas the secondary type may show multiple small foci and is frequently ilateral.

Case reports of primary renal actinomyscosis have been published by Israel 2 cases), Kleinschmidt, Kretschmer and Hibbs, Stanton, Kellock, Kunith, Racic, chneider, Prins, Mathé, Neumann, Peacock, Polayes and Lederer, Kindall, arl, Beregoff, Abbott, Kimball and Haining, Pinner, Hunt and Mayo, Moore nd Topper, Recht, Bedrna and Pavlika, Sixl, Cohen, Levin and Andrew.

The disease occurs at all ages, with a slightly greater incidence in males. Actino-nycosis bovis can be saprophytic in the body and may gain admission through he previously mentioned avenues. Renal involvement occurs by direct extension rom contiguous structures, or through the blood stream. Its occurrence follow-ng appendectomy is too frequent to be coincidental. Frequently, there is the istory of a persistent fistula and of renal involvement months or years later. Retroperitoneal extension downward from the lung or upward from the appendiceal or cecal region may occur, with or without renal involvement. Infection of the kidney may be secondary to a vertebral lesion with abscess formation.

Actinomyces bovis is a facultative anaerobe which can be cultured with difficulty. The varieties found on hay and grass are generally aerobic and consequently are not likely to be those responsible for actinomycosis. The colonies or sulphur granules in pus may be as large as 200–300 mu. in diameter with axial club shaped filaments at the edge. Gram stain reveals gram-positive, branching granular mycelia traversing the colony. The bulk of the colony, and the clubs, however, are gram negative and eosinophilic.

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[1] Read at annual meeting, Mid-Atlantic Section, American Urological Association, Washington, D. C., March 21, 1947.

Presented with the permission of the Medical Director, Veterans Administration who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

Actinomycosis is a chronic, suppurative disease characterized by multiloculated abscess formation and proliferation of fibrous and granulation tissue. As the process advances, there is induration of the involved tissues with ultimate degeneration and necrosis. The lesion may involve the entire kindey or may be localized to one segment or pole. Rarely, the lesion as a whole may soften and discharge its pus into the pelvis. Renal actinomycosis may start as a circumscribed lesion which progresses to a chronic carbuncle, later perforating to form a paranephric or perinephric abscess. The original lesions may occur as pyelonephritis, pyonephrosis, or in single or multiple cortical foci. With the formation of a perinephric abscess, the localizing clinical symptoms appear. Multiple fistulas with an intercommunicating network of channels may present in the lumbar, inguinal, femoral, gluteal, and thigh regions. There is a marked tendency to tissue destruction, such as bone, muscle and skin. Spontaneous healing of the renal lesion is unknown, and if the kidney is not removed surgically, the disease ultimately is fatal.

Microscopic examination reveals numerous pockets of pus consisting of polymorphonuclear leukocytes and containing the actinomyces colonies. Surrounding the abscess is a zone of granulation tissue infiltrated with numerous phagocytes, containing fat, round cells, plasma cells, and numerous fibroblasts. Beyond this, there is a dense fibrous tissue zone which infiltrates, distorts, and destroys the renal parenchyma. Many of the cases have a history of renal calculus or pyelonephritis, and following operative or cystoscopic procedures, develop renal actinomycosis.

One of the earliest symptoms is low grade intermittent fever, later associated with rigors and sweats. There are also anorexia, loss of weight, a rapid pulse, varying degrees of anemia, and leukocytosis. Later, localizing symptoms appear, including pain and tenderness in the costovertebral angle, upper abdominal rigidity, mass, edema in the lumbar region, intermittent hematuria, and pyuria. The voided urine, and that from the involved kidney usually show hematuria and pyuria. Actinomyces may be found in the urine, but is seldom reported. The kidney may be enlarged, fixed, displaced, or rotated. A perinephric abscess may form with its characteristic roentgenographic changes. Sinus tracts may be developed to the skin. Colonies of actinomyces may be seen in the pus as bright orange-yellow granules. In the absence of a draining sinus, sulphur granules in the pus, or involvement elsewhere, the diagnosis of renal actinomycosis is practically impossible and seldom suspected. Most cases are believed to be renal tumor, perinephric abscess, or tuberculosis, and cannot be differentiated clinically, except in the rare instance where actinomyces is found in the urine. The presence of fever is more in favor of infection than tumor. Tuberculosis of the kidney may be differentiated by finding acid-fast bacilli in the urine, and is not associated with perinephric abscess or fistulas. Suppurative pyonephrosis, carbuncle of the kidney, and pyelonephritis due to other organisms can be differentiated by isolating the responsible organism. In caries of the spine, characteristic bony changes may be seen. However, a survey of the literature revealed that almost all cases came to operation or autopsy with a diagnosis of either renal tumor or tubercubright yellow cortical masses about the size of corn kernels were also seen. A subcapsular nephrectomy was then performed, and the incision closed with adequate drainage. Immediately postoperative, 500 cc of citrated blood were given.

The specimen consisted of a right kidney measuring 18 by 7.5 by 5 cm. The urface of the lower two-thirds was irregular, showing numerous projecting nodules, with central abscess formation and a surrounding zone of congestion and hemorrhage (fig. 2). On section, the lower part of the kidney was occupied by a arge, irregular, multiloculated abscess, measuring 9 cm. in its greatest diameter. The abscess was composed of numerous small pockets containing yellow pus, with firm intervening tissue; the larger pockets varying from 1–2 cm. in diameter. The abscess wall had a translucent grey appearance, and was firm and rubbery n consistency. The pus was yellow, and, in some areas, rust colored streaks pene-

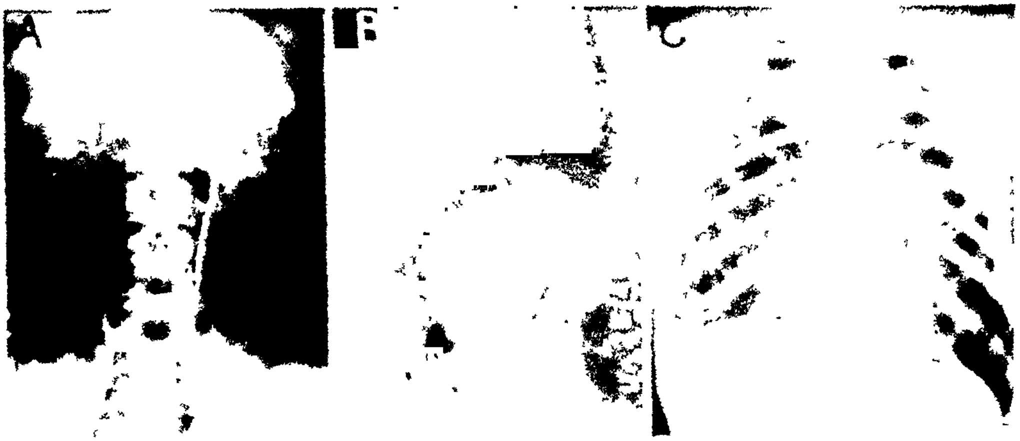

FIG. 1. A, bilateral retrograde pyelogram, showing distortion of right inferior calyx nd pelvis with displacement of right ureter. B, right lateral retrograde pyelogram, showing nterior displacement of ureter. C, roentgenogram of chest. Arrows point to metastatic oci in both lower lobes.

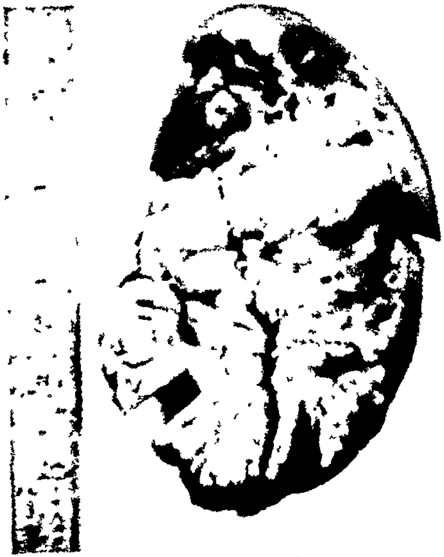

FIG. 2. Right kidney, showing multiloculated abscesses and destruction of renal parenhyma.

trated the granulation tissue Numerous sulphur granules were found in the pus Microscopic examination revealed extensive destruction of renal tissue with extensive abscess formation The latter contained a polymorphonuclear exudate with numerous large colonies of actinomyces (fig 3) These were irregularly rounded in shape varying from about 50 to 300 mu They stained with eosin, forming a homogeneous mat with surrounding radially arranged clubs Gram stain revealed coarsely granular gram positive delicate filaments traversing the colony The mat and the clubs were gram negative At the periphery of the abscess numerous fat laden phagocytes, round cells, plasma cells, and polymorphonuclear leucocytes invaded the dense fibrous tissue barrier The latter showed active fibroblastic proliferation The blood vessels showed marked obliterative endarteritis The pathologic diagnosis was renal actinomycosis

From November 26, 1946, and postoperatively until discharge on January 20 1947 (the forty eighth postoperative day) the patient received a total of approximately 20 5 million units of penicillin He also was given 2 liters of intravenous glucose daily the first 5 postoperative days Parenteral and oral multivitamins with iron therapy were prescribed liberally during entire hospitalization From November 26 to December 2 he received ⅓ gm sulfadiazine 4 times a day, and from December 2 to January 18 he was given ½ gm each of sulfadiazine and sulfathiazole The patient walked around the foot of his bed, unaided on the first postoperative day, gradually increasing his activity daily The temperature, which on admission spiked daily from 98 F to 103 6 F, fell to normal 48 hours after operation and except for a few minor transient elevations, remained normal since then Drainage from the incision quickly became serous and subsided Sutures and drains were all removed by the tenth postoperative day, and the incision was completely healed by the twenty first postoperative day Roentgen examination of the chest, taken on the eighth postoperative day, revealed complete disappearance of the nodules previously described On the eighteenth post operative day, a blood transfusion of 500 cc of citrated blood was given The

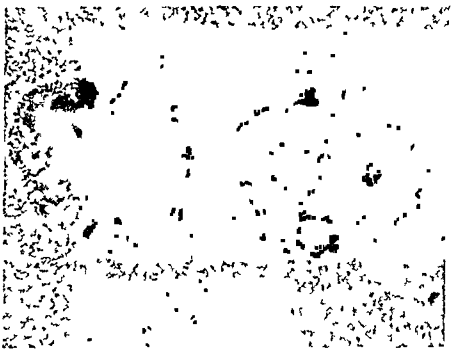

Fig 3 Photomicrograph, showing 2 colonies of actinomyces from one of the abscesses (AIP Accession 184263)

throcyte count, which was 3,500,000 per cu. mm., rose to 4,200,000 at the ne of discharge.

The patient was seen again on March 17, 1947. There were no complaints, and weighed 163 lbs. A urinalysis and complete blood count were within normal nits. The right iliocostal incisional scar was well healed and had remained so ce hospital discharge on January 20, 1947.

SUMMARY

The twenty-eighth case of primary or solitary actinomycosis is presented.

The clinical features, pathology and treatment of the disease are reviewed.

In addition to nephrectomy, the use of large doses of penicillin over a pronged period is recommended.

The adjuvant oral sulfonamides may also be of some value.

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THE ATROPHIC KIDNEY AND HYPERTENSION[1]

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In 1934 Goldblatt first reported his experiments which showed that impairment of the circulation in one kidney could cause hypertension. Three years later, in 1937, an apparent cure of hypertension by the removal of a diseased kidney was reported by Butler. Following Butler's original report, there have been many reports of cases in which the removal of a diseased kidney has had a favorable effect on high blood pressure. Some of these cases, however, were reported too soon following nephrectomy to enable one to say irrevocably that the hypertension was relieved. Nevertheless, enough evidence has been presented that one may definitely state that unilateral renal disease is a factor in the etiology of hypertension and that removal of the kidney will have a definitely beneficial outcome. The most favorable results have been reported when nephrectomy was performed for unilateral atrophic pyelonephritis.

We wish to report, briefly, 13 cases of unilateral atrophic pyelonephritis treated by nephrectomy for the purpose of relieving hypertension.

CASE REPORTS

Case 1. A woman, aged 24, entered Scott and White Clinic on August 21, 1939e A history of recurrent urinary tract infection during childhood was given. Thre years prior to examination she had delivered a full-term stillborn child, having had some elevation of blood pressure during pregnancy. The blood pressure remained high, i.e., 170 mm. Hg. systolic, until a few months before entrance when it rose to above 200 mm. Hg. Physical examination revealed a rapid pulse. Blood pressure at rest was 220/140. The fundi were normal, and there was no edema. A mass was palpable in the lower left quadrant. Cystoscopy revealed normal function from the right kidney and somewhat reduced function from the left. Urine from both kidneys was negative microscopically and on culture. The pyelogram revealed a normal right kidney; but the left kidney was overlying the left sacroiliac region; the calyces were blunted and the pelvis was lateral, the kidney being non-rotated. The blood urea was 27 mg. per cent, and the total phenolsulphonphthalein was 72 per cent in 2 hours. Left nephrectomy was done September 11, 1939. The pathological report showed an ectopic kidney, weighing 72 gm. Sections revealed subacute and chronic pyelonephritis with only slight arteriolar changes. There was complete hyalinization of a few glomeruli. Following surgery the blood pressure was 120/94, but gradually rose to 180/152 on dismissal October 3, 1939. She continued downhill and expired 6 months later.

Case 2. A male physician, 36 years of age, was registered in the clinic March 27, 1940, with a history of having noted mild dysuria 6 weeks previously. Uri-

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dizziness, headaches, and nausea. At about 2 years of age she had "pyelitis" for about 1 month, but subsequent urinalyses through the years were normal, and no symptoms of urinary disease were experienced. Examination revealed a systolic pressure of 210 and diastolic of 165. Marked retinitis was present. Urinalysis showed specific gravity 1.015; albumin, grade 3; occasional white cells and red blood cells. The hemoglobin was 10.5 gm. per 100 cc and the red blood cell count was 3,430,000. The blood urea was 39 mgs. per cent. Excretory urograms revealed excellent delineation of the right kidney which was normal; the left was poorly functioning and smaller than the right. Retrograde studies confirmed these findings. Since this patient's sister had apparently shown improvement, it was decided to offer her the possibility of relief, although the prognosis was definitely poor. On December 29, 1941, a left nephrectomy was done. The kidney weighed 40 gm., showed a marked sclerosis of the vessels, glomerular and tubular fibrosis with marked interstitial fibrosis. The larger blood vessels showed marked thickening of their walls, some with their lumen quite small or completely obliterated. Numerous masses of lymphocytes were scattered throughout. The essential pathological picture revealed the same as in the twin sister. Three weeks following surgery the blood pressure remained 170/130. The vision returned to normal and there were no headaches or dizziness. The patient felt quite well for 6 months, but the blood pressure gradually rose to 266/170. She expired 9 months following surgery.

Case 5. A girl, 19 years old, reported to the clinic January 13, 1942, complaining of headaches. For a year prior to entrance, every 2 to 3 weeks she would have a dull frontal pain, relieved temporarily by aspirin or reclining. Later she would have throbbing occipital headaches which would last for 2 or 3 days. There was a history of urinary tract infection at the age of 3, which was treated cystoscopically, and the right kidney was thought to be tuberculous. At the age of 13 the blood pressure was elevated, but she was told that this was of no consequence, since it was probably emotional. Examination revealed the resting blood pressure to be 154/110. A cold pressor test elevated the systolic to 180 and the diastolic to 150. The lowest resting blood pressure was found to be 140/100. The eyegrounds were normal. Urinalysis showed a specific gravity of 1.015, and was chemically and microscopically negative. The blood urea was 20 mg. per cent. Urea maximum clearance was 104 per cent. A roentgenogram showed the left kidney to be small. Cystoscopic studies revealed normal function from the right kidney with poor function from the left. The pyelograms showed a normal right kidney, but on the left the calyces were blunted, the kidney contracted, and very little cortex was present. Left nephrectomy was done January 28, 1942. The kidney weighed 38 gm. Externally it was rough and nodular, the pelvis showing marked scarring. Sections showed extensive destruction of all functional tissue, and marked foci of chronic inflammation. There was thickening of the vessels in all degrees, though few were completely obliterated. The blood pressure 1 month following surgery was 158/100, and 4 months later was 150/110. However, the patient was symptom free, and the blood pressure remained at this level. She married and later became pregnant, at which time there was a progressive increase in the blood pressure. In October, 1945 she

Urinalysis showed a specific gravity of 1.017, a faint trace of albu- v white blood cells. The blood urea was 19 mg. per cent. X-rays ıall renal shadow on the right. Excretory urogram showed normal erally, the right kidney mass being small, with evident hypertrophy Cystoscopic examination revealed a normal bladder and negative oth kidneys. Phenolsulphonphthalein excretion was 15 per cent and 4.5 per cent from the right in 15 minutes. Nephrectomy was arch 24, 1945. The kidney weighed 58 gm. The cortex was quite was a rather marked chronic pyelonephritis present and many l tubules showed little cellular structure remaining, being replaced material. There was a marked sclerosis of the vessels. She was nonths later, the blood pressure at rest was 154/90. This patient prehensive and nervous at all times, with a markedly varying pres- er, at rest it was much lower than before surgery. At the present od pressure is from 130/80 to 170/100, depending upon her mental e. She complains of no symptoms referable to hypertension.

A single girl, 16 years of age, came to the clinic September 4, 1945. tory revealed that for 3 months previously she had noticed blurring At that time retinal hemorrhage and an elevated blood pressure were ere was no history of urinary tract infection. Examination revealed sure of 202/130. The eye grounds showed an old hemorrhage in the e. The voided urine had a specific gravity of 1.010, a trace of albu- as microscopically negative. The blood urea was 20 mg. per cent. pic examination the urine was negative and the function of the left kid- arkedly impaired. Retrograde pyelograms revealed a small atrophic ne left with clubbing of the lower calyces. The right kidney was some- ged, but showed a normal pelvis and calyces. On October 10, 1945, pressure was 204/154. Nephrectomy was done October 15, 1945. en weighed 50 gm. Microscopic sections showed numerous areas of ction and marked replacement of the normal structures by fibrosis. e several small cysts present in the cortical structure surrounded by fection. The blood pressure at the time of dismissal was 128/86. arried in 1947, and pregnancy followed. Two years following surgery, vas about 3 months pregnant, her blood pressure was 148/92. Her sure steadily rose to 190/120, and she delivered a stillborn infant at 8 estation. Six weeks following delivery the blood pressure returned to d 6 months later was 140/90.

A woman, aged 36, was registered in the clinic September 27, 1944, ef complaint of high blood pressure. Three years before entry, when pregnant, she was found to have an elevation of blood pressure to 170 After delivery, hypertension persisted, but was quite variable, and was duced by rest and sedation. She had some vertigo and occasional headaches when her pressure was high. There was no history sugges- vious renal disease. Upon examination the systolic pressure was found om 130 to 150 with the diastolic remaining at 88 mm. Hg. Urinalysis revealed the specific gravity to be 1.015, and was chemically negative. There was grade I pus in the voided urine. The blood urea was 21 mg. per cent. Excretory urograms showed a normal right kidney with no function on the left. Cystoscopic studies revealed a negative urine and the right kidney completely normal. No ureter could be found on the left. In the left renal position there was an area of calcification in an apparently atrophic kidney. Nephrectomy was done November 10, 1944. The kidney weighed 25 gm. When opened, the kidney consisted of numerous dilated spaces filled with a substance resembling curdled milk. The majority of these spaces were calcified. The normal structure was almost totally destroyed with evidence of marked arteriolar sclerosis. Two years following surgery she reported complete relief from vertigo and headaches, and the blood pressure was consistently around 126/72.

Case 13. A 42 year old woman was first seen December 11, 1941, complaining of recurrent attacks of pain in the left upper quadrant. Her blood pressure was 126/80, and a small atrophic left kidney was found which was nonfunctioning There was no history of infection, and none was found at this examination. A left nephrectomy was advised, but refused. The patient returned in February 1947. Pain in the left upper quadrant still persisted, and in addition she had developed headaches and vertigo. Upon examination the systolic pressure was 168 and the diastolic 100. The urine had a specific gravity of 1.024, and the blood urea was normal. Cystoscopic examination showed no infection present, but a nonfunctioning left kidney and a normal, large kidney on the right. A nephrectomy was done January 28, 1947. The specimen weighed 6 gm. and measured 3.5 by 2.5 by 1 cm. The pelvis of the kidney was quite small, measuring 1.5 cm. at its greatest diameter; the parenchyma was 1 cm. in its greatest thickness. There was moderate sclerosis of the vessels. At the present time, 30 months following surgery, the blood pressure is 150/100. The headaches and vertigo, in addition to the pain in the side, were relieved.

COMMENT

In 7 of the 13 cases the blood pressure returned to normal and has remained so from 2 to 9½ years. In 5 cases the blood pressure remained the same, 3 of the patients dying at 6 months, 9 months, and 4 years, respectively. In 1 case the blood pressure remained the same after 18 months, though the symptoms were definitely relieved.

The average age of this group of patients is 28 years, there being 4 in the second decade of life, 4 in the third, 3 in the fourth, and 2 in the fifth decade. The average duration of known hypertension is 3 years; the shortest duration, less than 1 year; and the longest, approximately 8 years. The group having good results shows an average duration of 2 years, and the group with poor results shows an average duration of 3 years.

In 6 of the 7 cases with good results the opposite kidney was considered hypertrophied, while this was not noted in any patient with poor results. Of the 7 cases reported having a return to normal blood pressure the function of the atrophic kidney was normal in 1 case, recorded poor in 4 cases, and nonfunction-

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It is believed that over a period of time irreversible changes occur in the opposite kidney that would prevent a return to its normal state

Braasch in a study of 1000 cases of hypertension found only 2 5 per cent with unilateral renal changes, and Ratliff in a review of 1350 cases found 5 per cent possible candidates for nephrectomy for the relief of the hypertension Applying this to the estimated number of hypertensives in the United States would indicate that there are thirty to sixty thousand persons that may be relieved by nephrectomy We believe that every patient under 50 years of age with an essential type of hypertension should have an excretory urogram and more complete urologic study when indicated

SUMMARY

Thirteen cases in which removal of an atrophic kidney for relief of hypertension has been performed are reported Certain criteria are suggested

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UNILATERAL MALIGNANT NEPHROSCLEROSIS

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in the renal genesis of essential hypertension has received support in uarters. There are many valid objections to identifying experimental ·pertension with the essential type and until these criticisms are met, ·t defer acceptance of this concept. It is not the province of this report nt the evidence in either direction. More specifically, it is our aim to a unique example of unilateral malignant nephrosclerosis resulting from ·nce with the blood supply of the contralateral kidney.

clinical counterparts of experimental renal hypertension are on occasion ı nature is well established.[1, 2, 3, 4] Identification of such cases must be to those closely analagous to or identical with the established experi- situations. Thus, one may consider only those instances presenting evi- f partial occlusion of one or both main renal arteries, marked narrowing ·enal vascular bed, or perirenal constriction in which the renal disease ed the hypertension. The following case, we believe, adequately satisfies ·iteria.

CASE REPORT

., 32 year old white man, was admitted to the Psychiatric Institute of nds Hospital December 9, 1936 after attempting suicide by venesection. ear he had suffered from severe intermittent pain in the left foot and thigh ıated by walking. Excessive alcohol intake was denied and he admitted king one package of cigarettes a day.

·ical examination disclosed an underdeveloped, malnourished patient who appear acutely ill. The heart was not enlarged, the sounds were of good and no murmurs were audible. The blood pressure was 130/70. The re cold, slightly swollen and of a peculiar cyanotic hue. Increased cyanosis dependent position and blanching on elevation were noted. No pulsations alpable in the left dorsalis pedis or posterior tibial arteries. On the right, lsations in these vessels were weak. Good pulsations were felt in the radial s which were firm and somewhat beaded. There was slight muscle atrophy left calf and thigh. Oscillometric studies of the extremities confirmed the l impression of marked impairment of the circulation in the left leg with changes on the right. Oscillometric readings showed no improvement in tory function following novocaine spinal anesthesia.

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sclerosis. Arch. Int. Med., 66: 541, 1940 (case 1).

Laboratory studies including blood count, urine, phenolsulphonphthalein excretion, ESR, blood chemistry and blood Kahn were all within normal limits

The patient experienced only slight relief following therapy and was discharged March 10, 1937 with the diagnosis of thrombo-angiitis obliterans

On re admission in March 1938 he stated that during the interval he was unable to walk even short distances because of the cramplike muscle pains in his extremities The heart was not enlarged, sounds were of fair quality and no murmurs were heard The second pulmonic sound was louder than the aortic The blood pressure was 128/80 There was slight atrophy of the left thigh and leg The feet were cold, blanched on elevation and assumed a bluish cyanotic hue in the dependent position with bulging of the superficial veins The dorsalis pedis and posterior tibial vessels were not palpable on either side The right femoral pulse was stronger than the left

An electrocardiogram showed no significant change Again all laboratory investigations were found to be normal There was slight improvement and some relief of the intermittent claudication following therapy He was discharged May 27, 1938 with a diagnosis of thrombo-angiitis obliterans

In May 1944 he was re admitted complaining of a chronic ulcer of the left ankle resulting from an injury 6 months previously Intermittent claudication and precordial pain were present on exertion Examination revealed the pulse rate to be 90 per minute, and blood pressure 163/100 The cardiac examination was otherwise negative An ulcer was present over the right internal malleolus The signs of peripheral vascular disease previously noted were unchanged The deep reflexes of both lower extremities and the abdominals were absent, but no pathological reflexes were elicited

Laboratory examination revealed a slight normochromic anemia and a white blood cell count of 8,550 with a normal differential All further laboratory studies including renal function tests and chemistries were again normal

The leg ulcer responded to therapy and healed completely by June 14, 1944 when he was discharged

On October 16, 1944 he was admitted to another institution because of hematemesis He had had mild attacks of indigestion for several months, and for three days before admission had vomited small amounts of blood His pulse rate was 90 per minute and the blood pressure was 140/95 He had slight epigastric tenderness but otherwise the findings were as noted previously

Again a mild normochromic anemia was present, but the white count and differential were not abnormal The urine specific gravity was 1 018 and 1 014 There was 2 plus albumin and many red blood cells with 3 or 4 white blood cells seen in each high power field The Kline test was negative A gastro intestinal series revealed a duodenal ulcer He improved and was discharged December 3, 1944 with a diagnosis of peptic ulcer of the duodenum

On January 24, 1945 he again returned to the above institution complaining of weakness, headache, and back pain The interim history is significant only in that he had eaten poorly and had taken alcohol presumably to excess On admission he was confused and rebellious His blood pressure was 160/100 and as epigastric tenderness. He was treated with Amphojel, Meulengracht d phenobarbital and was transferred to the Westchester County Home ary 31, 1945, with the diagnoses of 1) peptic ulcer and 2) probable delirmens.

inal admission took place on February 9, 1945 when he complained of the arms, legs and abdomen as well as occipital headache and impair- vision. As before, he experienced claudication on walking short dis-

cal examination showed a somewhat undernourished, chronically ill no acute distress. Slight icterus of the skin and sclerae was noted. The te was 120, respirations 16 per minute, temperature 99.6 F, and the blood 210/130. Funduscopic examination showed evidence of hypertensive thy grade 3 (Keith Wagener). The heart was not enlarged and the sounds rmal. The rhythm was regular and no murmurs were heard. There was zed abdominal tenderness. The liver edge was palpable 3 finger breadths ne right costal margin. The left leg was perceptibly thinner than the neasuring 2 cm. less in circumference at the calf level. The lower limbs d much as before, and pulsations in the left popliteal, dorsalis pedis and r tibial arteries were not felt. No evidence of extreme arteriosclerosis md on x-ray of the extremities. Varicosities, some thrombosed, were ent over the medial aspect of each thigh. Pigmentation of the skin and oid eruption about both ankles were present. The blood pressure in the g was 210/110, but none was obtainable on the left. Deep reflexes were n the upper extremities, but absent in the lower. There was some loss of ial pain-touch sensation in both lower limbs.

lmission the icterus index was 15, the urine negative for bile, and a Hangar tion test was normal. The icterus index fell rapidly so that 1 week after on it was only 5, while the urine was still negative for bile. The Hangar tion was repeated and was again negative. Urine urobilinogen was pres- a normal titer.

clinical course continued steadily downhill with the development of ssive elevation in the blood nonprotein nitrogen and creatinine from norvels to respectively 75 mg. per cent and 6 mg. per cent. Many urines l specific gravity to vary between 1.004 and 1.012, most often between nd. 1012. Persistent 4 plus proteinuria was present. Microscopic examina- the urine revealed an occasional white blood cell, few to many red blood nd moderate numbers of hyaline and waxy casts. Total blood proteins .4 gm. per cent, albumin 4 per cent, globulin 2.4 per cent. With the pro- n of uremia, the patient developed a severe normocytic anemia which ded temporarily to transfusion.

roximately 2 weeks before death a sudden onset of dyspnoea, cyanosis, ss of the chest and a cough productive of pink sputum was noted. This sociated with an elevation of temperature to 103 F, the first evidence of following admission. This suggested a pulmonary embolus, probably eral in origin.

The electrocardiogram on admission revealed sinus tachycardia, left axis deviation, and a PR interval of 0 20 seconds Three weeks later the PR interval was 0 21 seconds and changes suggesting increased heart muscle damage were recorded No suggestive electrocardiographic changes were noted following the presumed embolic episode

X-ray examination of the chest March 21, 1945 showed an increase in the size of the heart, particularly the left ventricle, and an exudative infiltration in the left upper lobe with marked congestive changes in this region as well as throughout the right central lung field Sputum studies showed type 3 pneumococcus after mouse inoculation A blood culture was negative In spite of penicillin therapy the patient continued to fail rapidly His temperature remained persistently elevated, as did his total white count Death occurred on March 30, 1945

One observer, in an attempt to reconcile the long standing thrombotic manifestations with the onset of a malignant form of hypertension offered a diagnosis of renal artery thrombosis, thus suggesting a clinical counterpart of the Goldblatt experiment This diagnosis was ultimately confirmed at autopsy

The autopsy was performed 2 hours postmortem The heart weighed 400 gm The left ventricle was dilated and hypertrophied, measuring 1 8 cm in thickness The valves were competent and the cusps thin The endocardium and myocardium were not remarkable The ascending aorta was not remarkable, but in the lower thoracic and abdominal portions, there were several calcified intimal plaques and an adherent thrombus The thrombus did not seriously narrow the lumen of the aorta, but extended to occlude the ostium of the left renal artery When opened, this vessel was seen to be occluded for several centimeters distal to its origin by pale adherent thrombus The right renal artery was not remarkable, its ostium unobstructed

The right lung weighed 550 gm , and the left 525 gm The visceral pleura was thickened by fibrous adhesions Numerous shotty areas of consolidation, most numerous in the upper lobes, were felt On section, these areas were dry and pale with a ground glass luster The bronchi were congested, while the blood vessels and hilar lymph nodes were not remarkable

No free fluid was present in the abdominal cavity The liver weighed 1600 gm , and on section the lobular pattern was made out with difficulty The gallbladder and extrahepatic ducts appeared normal The spleen weighed 200 gm , and on section its surface was quite dry and the follicles indistinct The adrenals and pancreas were grossly unaltered A round, flattened area, suggesting a healed ulcer, was seen in the posterior wall of the first part of the duodenum

The right kidney weighed 175 gm and the capsule stripped with moderate to marked difficulty The surface was granular and the cut surface glazed and dull red The corticomedullary demarcation was obscured The left kidney was smaller, weighing 100 gm It appeared congested and on section, the cortex was narrowed, but the architecture was not appreciably altered No infarction was observed The lower urinary and genital tracts were not remarkable

The vertebral marrow was deep red

The peripheral vessels examined (lower extremities) appeared grossly within normal limits.

The brain weighed 1350 gm. The vessels were uniformly thin. After fixation the brain and spinal cord were sectioned and no significant changes were seen.

Microscopic examination of the heart showed no significant valvular changes and only a few small foci of fibrous replacement of myocardium were seen. In the roots of the pulmonary artery and aorta the vasa vasorum were often ringed by clusters of mononuclear cells.

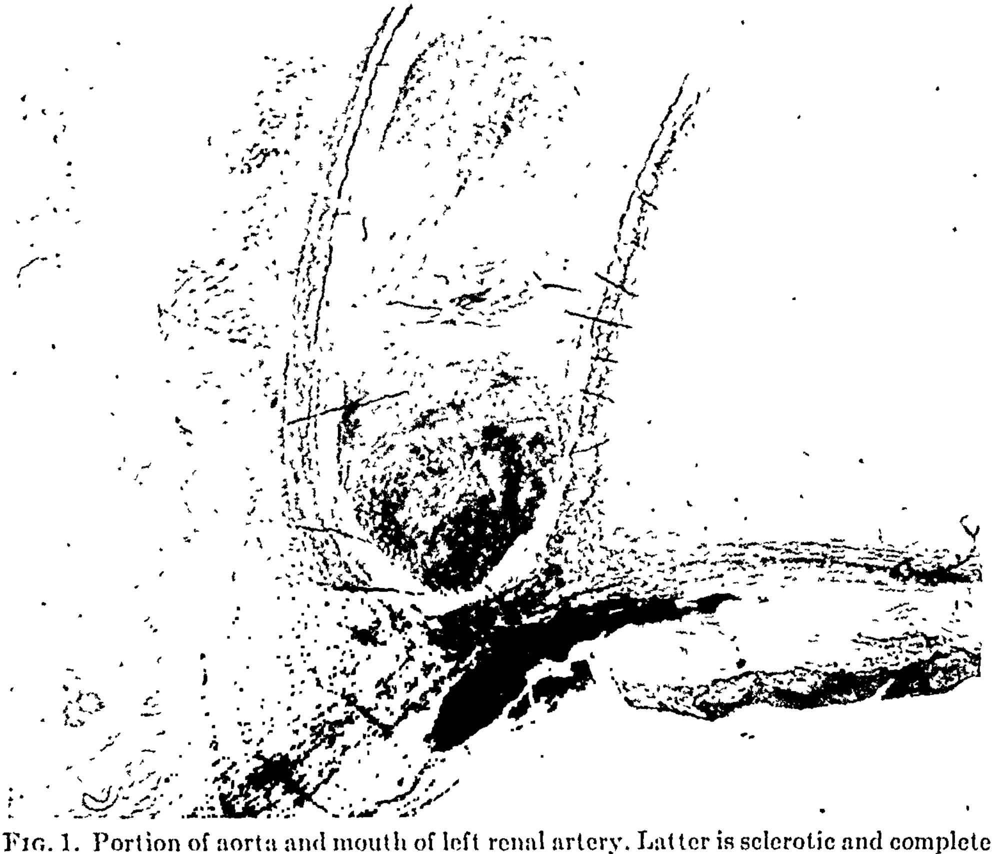

FIG. 1. Portion of aorta and mouth of left renal artery. Latter is sclerotic and completely occluded by recent and old masses of thrombus material. Aorta is markedly sclerotic and intima is covered with hyalinized thrombus material. (Verhoeff's elastic tissue stain.)

In the aorta and left renal artery (fig. 1) atheromatous plaques, which irregularly thickened the intima, were overlaid by masses of thrombus material exhibiting extensive hyalinization, organization and calcification. The vessel wall beneath was markedly sclerotic and thinned and a mononuclear, principally lymphocytic, infiltrate was present in the media and adventitia. The mouth of the left renal artery was completely occluded (in the sections examined). Here too, the thickened atheromatous intima was covered by ancient hyalinized thrombus material which all but filled the lumen. The occlusion was completed by a recent eccentrically placed thrombus.

A marked difference was apparent in the microscopic picture of each kidney. In the right kidney (figs. 2 and 3) there was extensive vascular, glomerular and

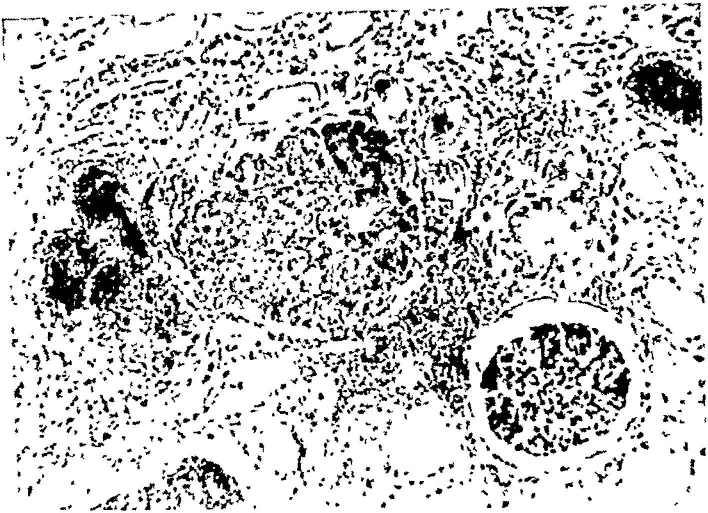

FIG. 2. Section of right kidney. Fibrinoid arteriolonecrosis, hemorrhagic infarction of a glomerulus, and severe alteration of parenchymal elements are noted. (Hematoxylin and eosin stain.)

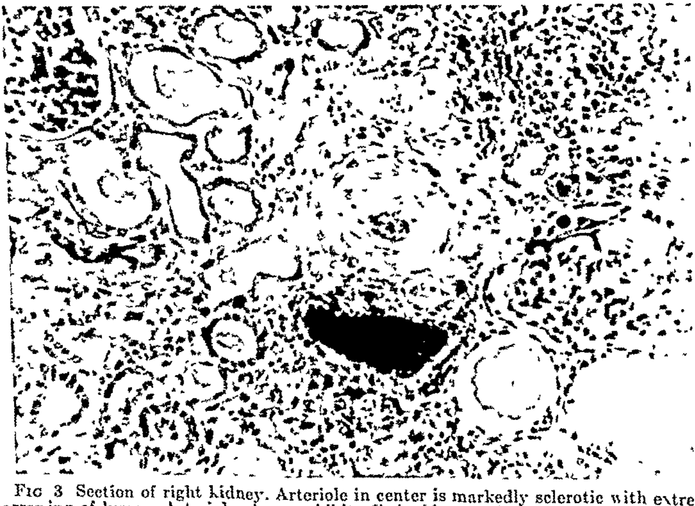

FIG 3 Section of right kidney. Arteriole in center is markedly sclerotic with extreme narrowing of lumen Arteriole above exhibits fibrinoid necrosis, but vein is not altered. (Hematoxylin and eosin stain.)

tubular damage. The arterioles, small and medium sized arteries exhibited marked intimal thickening due to endothelial hyperplasia and subintimal fibrosis. Fibrinoid necrosis of part or even of the entire circumference of vessels was noted. Fibrinoid change was apparent in some glomeruli and some capillary loops contained hyaline thrombi. The glomeruli were cellular, relatively avascular, and some tufts, or on occasion, complete glomeruli were necrotic and haemorrhagic. The tubular epithelium was flattened in many places and colloid droplet degeneration was observed. Hyaline, granular, or red cell casts were present in many tubules. A widespread interstitial lymphocytic infiltrate accompanied these changes.

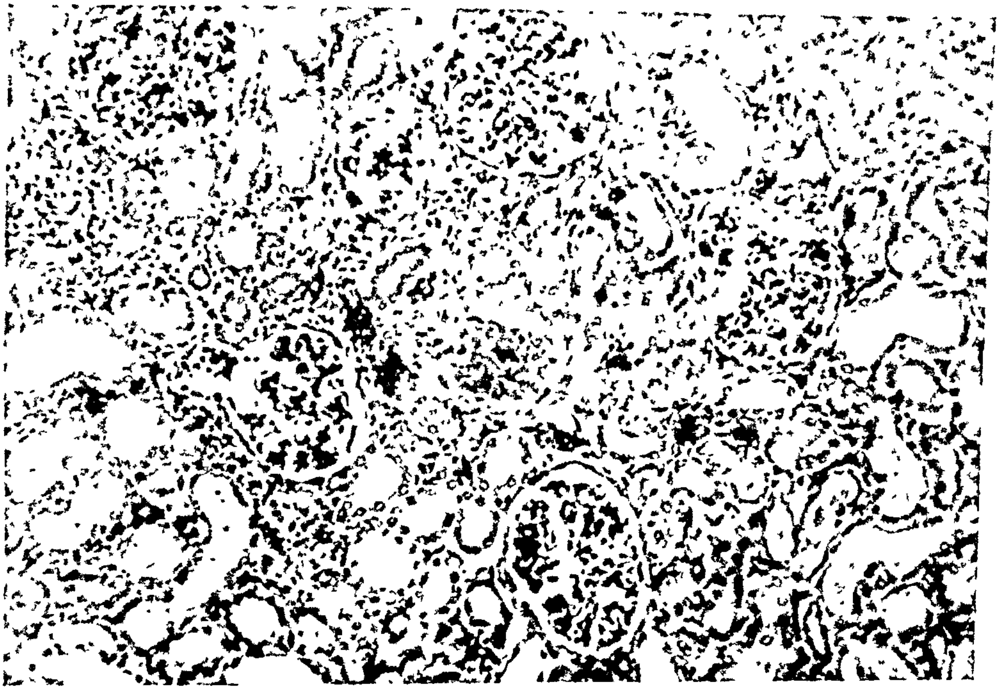

FIG. 4. Section of left kidney. Vascular sclerosis is not present, and renal elements are not significantly altered. (Hematoxylin and eosin stain.)

In the left kidney (fig. 4), the arteries and arterioles showed few changes except for slight subintimal fibrosis in an occasional vessel. Focal atrophy and degeneration of the renal parenchyma was noted in scattered areas. In these wedge-shaped foci the inflammatory infiltrate was predominantly polymorphonuclear with a considerable mononuclear representation, and an occasional glomerulus was necrotic. Clusters of tubules exhibited slight dilatation. No bacteria were identified in sections stained with a modified Brown and Brenn stain.

The posterior tibial artery (fig. 5) was filled by an organized, recanalized thrombus whose endothelial channels were dilated and engorged. The well preserved elastica interna was reduplicated in some areas, and there was some medial and adventitial fibrosis. A nearby vein had been thrombosed, but was now recanalized. Nerves, including a section of posterior tibial nerve, showed no evidence of participation in this process.

A widespread pneumonic process was evident in the lungs. The alveoli were filled with a fibrinous or fibrinopurulent exudate with evidence of intra-alveolar organization in many areas. Some smaller arteries contained recanalized thrombi (embolic?) while other vessels showed some intimal proliferation.

In the liver scattered foci were seen in which liver cells had dropped out, a condensation of the stroma had been effected, and a few lymphocytes had accumulated.

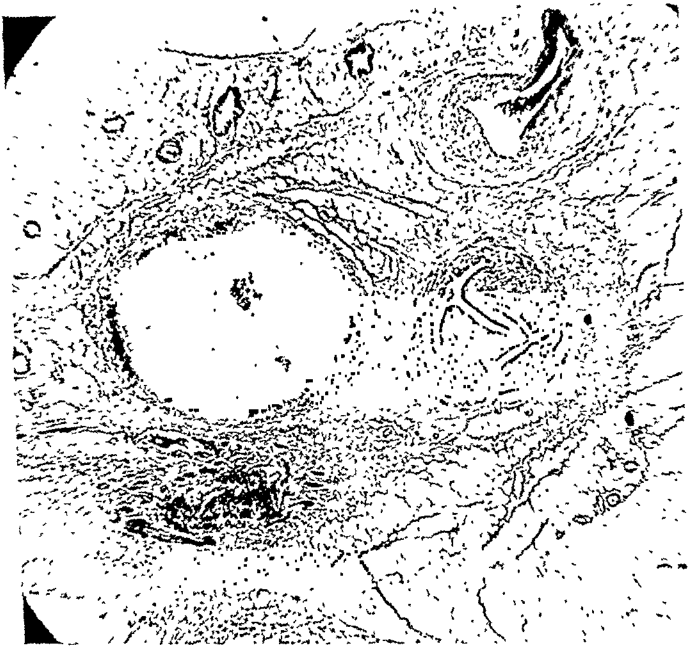

FIG. 5. Section of posterior tibial artery and ve[illegible] a hyperemic recanalized thrombus. Vein, too, is filled with reca[illegible] is perivascular fibrosis, but inflammatory component is meager. [illegible] stain.)

In the spleen the red pulp was congested and contained many hemosiderin bearing macrophages. Slight arterial and arteriolar sclerosis was present.

The pancreas and adrenal showed no significant parenchymal change, although there was some arterial and arteriolarsclerosis.

In the duodenum a healed ulcer in which the glands rested directly on the muscularis was seen. The latter was partially and completely replaced by fibrous tissue. A nearby branch of the pancreatic duodenal artery was filled with recanalized thrombus.

In the brain a small area of encephalomalacia was seen in the region of the left basal ganglia. The vessels were not grossly unusual.

The final diagnosis was 1) atherosclerosis of aorta with calcification and thrombosis; 2) occlusion of left renal artery due to atherosclerosis and thrombosis, recent and old; 3) malignant nephrosclerosis of right kidney; 4) focal atrophy of left kidney; 5) hypertrophy and dilatation of heart; 6) thrombo-angiitis obliterans of lower extremities; 7) thrombi in pulmonary arteries, organized and recanalized (emboli?); 8) organizing pneumonia, bilateral; 9) ulcer of duodenum, healed; 10) thrombosis of branch of pancreatico-duodenal artery, organized and recanalized; 11) focal necrosis of liver, old; 12) encephalomalacia region of left basal ganglia; 13) tuberculosis of left lung, inactive; 14) fibrous pleural adhesions.

DISCUSSION

Goldblatt has shown that interference with the blood flow to the kidneys results in elevation of blood pressure.[5, 6, 7] This hypertension shares many of the features seen in the syndrome of essential hypertension. A more intensified form of this syndrome comparable to the malignant form in man was achieved experimentally by tying off the ureter of the contralateral kidney, removing the contralateral kidney or severely constricting the renal arteries. Fibrinoid necrosis of renal vessels or of vessels of other organs was the most prominent feature. However, the kidney whose vessel was constricted was spared these changes. Goldblatt was of the opinion that both severe hypertension and severe disturbance of renal excretory function are necessary for the production of arteriolonecrosis in man as well as in dogs. Byrom and Wilson,[8] however, have been able to produce in rats, in the absence of renal insufficiency, the changes of malignant nephrosclerosis by constricting one renal artery. It was their opinion that renal dysfunction is not a necessary prerequisite, but that the malignant phase may be induced by severe vasoconstriction of one renal artery and rapid rise in blood pressure. The same factors play a determining role in the change from benign "essential" hypertension to the malignant form in man.

The literature contains a number of reports in which intrinsic and extrinsic lesions have interfered with renal blood flow with resultant hypertension. Yuile,[9] in a recent review, concluded that renal and aortic atheromatous plaques are usually secondary to essential hypertension except in the rare case where renal arteriolosclerosis is absent. In our case, arteriolosclerosis is absent in the kidney whose main artery is obstructed. Renal arterial thrombosis or embolism in reports by Fishberg[10] and Yuile[9] has been associated with the onset of hypertension. The sudden and unexpected appearance of hypertension in a patient who has manifested thrombotic phenomena should suggest, as it did in this case,

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[5] Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W.: Studies on experimental hypertension. I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J. Exp. Med., 59: 347, 1934.

[6] Goldblatt, H.: Studies in experimental hypertension. VIII The production of the malignant phase of hypertension. J. Exp. Med., 67: 809, 1938.

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[10] Fishberg, A. M.: Hypertension due to renal embolism. J. A. M. A., 119: 551, 1942.

the presence of an obstructive lesion, thrombus or embolus, in the main renal artery or vein.

Unilateral malignant nephrosclerosis is an extremely rare finding in man. Saphir and Ballinger[4] presented a detailed report of hypertension associated in the thrombosis of the left renal artery following an accident. The patient died in uremia. The left kidney was unaltered except for a small area of infarction. The right renal artery was patent and its kidney presented the typical picture of malignant nephrosclerosis. Davson[1] reported similar findings in a patient with hydatid cyst of the right kidney. The left renal artery was spared and this kidney presented the typical picture of malignant nephrosclerosis.

In our patient extensive atherosclerosis was observed in the lower thoracic and abdominal aorta and on the athermatous plaques thrombi had been deposited. A similar process involved the mouth of the left renal artery. Here an old partially calcified plaque and superimposed old hyalinized thrombus markedly narrowed the lumen. The obstruction to the blood flow in this renal artery was of some standing, and the changes in plaque and overlying thrombus indicate that they may well have antedated the onset of hypertension. Recently, probably in the latter stages of his last illness, a fresh thrombus was superimposed on the old one, markedly aggravating the obstruction so that in the section examined it appeared completely occluded. The initial insult in this vessel presumably led to "altered renal hemodynamics" which was the initiating impulse in the development of his hypertension. Later, the circulation in this narrowed vessel was not sufficient for the metabolic needs of this organ and focal areas of atrophy supervened, but little or no arterial or arteriolarsclerosis was seen in this kidney. The right kidney presented an entirely different picture in which the markedly thickened and sclerotic arteries and arterioles, many of the latter exhibiting arterial fibrinoid necrosis, were predominant. Widespread glomerular and tubular change, recent and old, added to the picture of severe renal damage.

The clinical diagnosis of thrombo-angiitis obliterans of the lower extremities was borne out by the autopsy findings The involvement of the smaller pulmonary arteries by organized and recanalized thrombi probably represents embolization from the lower extremities. Histologically the vascular lesions obviously antedated the recent organizing pneumonia.

SUMMARY

A case of unilateral malignant nephrosclerosis secondary to vascular obstruction in the contralateral renal artery is reported.

Malignant hypertension occurring in the presence of a diffuse vascular disease should suggest, as it did in this instance, a clinical diagnosis of renal artery thrombosis.

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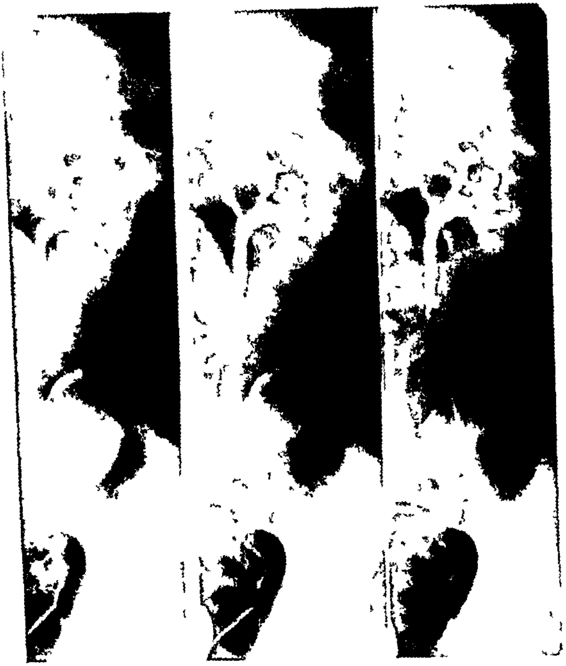

FIG 1 Left ureteropyelogram with varying amounts of opaque medium Angioma, found at surgery, in superior calyx, is not evident in roentgenograms

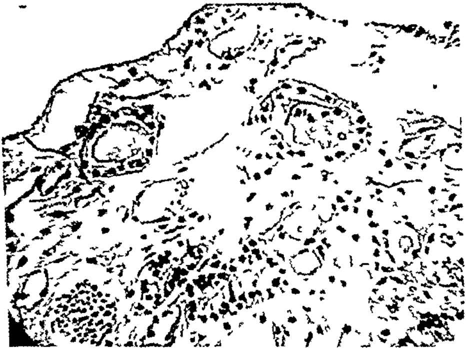

FIG 2 Angiomatous lesion of papilla, showing newly formed, thin walled blood spaces

The patient was not seen again until 6 years later, complaining of the same symptoms, which had been present constantly for 3 years prior to re-admission.

For 3 or 4 weeks the pain had been incapacitating and he had passed many small string-like clots. The findings in the general physical examination, urine, blood chemistry, diagnostic study and pyelograms were essentially the same as previously noted in 1941.

In view of the incapacitating pain and continuing hemorrhage, a left nephrectomy was performed on February 9, 1948, after exploration of the left kidney revealed only bloody urine in the renal pelvis. The patient had an uneventful postoperative course and was discharged from the hospital on the seventh postoperative day.

The pathological report of the surgical tissue was as follows: Grossly, the kidney was normal in size, shape and color, but with persistent lobulation. The papilla, in the superior calyx, bulged slightly and the tip was more reddened than normally noted. The pelvis and ureter were normal but contained many flecks of old blood. Microscopically, the section through the previously described papilla showed many thin walled vessels engorged with blood. There was a peripheral area composed of newly formed thin walled blood spaces which was typical of a small angioma. This pathology was sufficient to account for the hemorrhage. Diagnosis: Hemangioma of renal papilla. (See figure 2.)

The patient has been followed closely in the clinic since surgery, and was last seen in July of this year, at which time the right kidney was rechecked and found to be entirely normal.

SUMMARY

A very brief review of the literature, with report of a case of small renal hemangioma, is made for the purpose of stressing this pathological change as a cause of renal pain and hematuria in the absence of significant radiological findings. It is thought that perhaps these smaller hemangiomata are much more frequently present than the literature would indicate. The writer will be ever on guard to eradicate these smaller lesions with conservative surgical procedures, short of nephrectomy.

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LYMPHOSARCOMA OF THE KIDNEY: CASE REPORT[1]

CLAY O. MILLER

A recent review of the literature on lymphosarcoma of the kidney reveals that this condition has never been proven to be primary in the kidney and that preoperative diagnosis has never been made.

Sarcoma of the kidney is rare. However, it occurs equally in both sexes, especially in the 10 to 60 age group and equally on both sides of the body. The prognosis is poor. X-ray has been found of no therapeutic value, although lymphosarcoma is said to be radio sensitive.

It is the consensus that many sections of the tumor should be examined in order to rule out the growing edge of a hypernephroma and Wilms tumor of the adult.

The following report of a case of lymphosarcoma of the kidney demonstrates the difficulty encountered in preoperative diagnosis.

CASE REPORT

Mrs. E. A., aged 50, entered West Suburban Hospital June 3, 1948, acutely ill. Her chief complaints were pain in the back, on the right side, of 5 months' duration, periodic attacks of vomiting, also for 5 months, and dysuria for the past 4 months. She was not mentally alert and could not understand or answer questions coherently. Her husband stated that she had become ill suddenly 5 months previously, the illness characterized by nausea, prostration and vomiting. The vomiting had continued with little interruption for a period of about 5 weeks, the pain in the right side of back and loin was almost continuous from the onset. Approximately 3 weeks after onset of illness, dysuria had developed and was quite constant, characterized by sudden, intermittent interruption of micturition. Her appetite had been very poor since the onset of illness and there had been an increased desire for fluids. She had been bedridden during the first month but did not lose much weight or strength. During the second month there was an increase in the severity of the symptoms and she began to have chills and fever. A complete general and urological examination elsewhere indicated that all her trouble was confined to the urinary tract. After a stay in the hospital she returned home. She had improved and was able to be up and about. At the beginning of the fourth month there was a relapse with aggravation of previous symptoms and she became completely bedridden. In the subsequent 6 weeks there was a general decline but with little loss of weight. The past and family history were negative.

The abdomen was negative except for a firm, palpable mass in right loin, extending well toward the midline and to the brim of the pelvis, which was tender to palpation. The blood pressure was 150/85. The patient appeared drowsy and responded very slowly to questions.

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[1] Read at annual meeting, North Central Section, American Urological Association, Des Moines, Iowa, October 29, 1948.

The abnormal laboratory findings were: albumin, a trace; sugar, 20 drop reduction; red blood cells, 2,980,000; hemoglobin, 9.25 grams—54 per cent; nonprotein nitrogen 322 mg. per 100 cc, and creatin, 18 mg. per 100 cc.

The patient was given 500 cc whole blood (citrated) every other day until her red blood count rose from 2,980,000 to 4,210,000. Intravenous fluids consisting of 3000 cc of 10 per cent glucose in sterile distilled water and 1000 cc of 10 per cent glucose in normal saline were given daily until the day of surgery, at which time it was reduced to 2000 cc.

The urinary output gradually increased from 840 cc on the day of admission to 4200 cc on the seventh hospital day, when the blood chemistry findings showed a marked reduction in both the nonprotein nitrogen and creatinin; the former reading being 92 mg. per 100 cc; the latter 4 mg. per 100 cc.

Cystoscopy showed the bladder to be normal throughout; No. 6 catheters were passed up each ureter without difficulty. Phenolsulphonphthalein appeared in good concentration on the left side in 4 minutes; no dye appeared on the right side in 18 minutes.

A right nephrectomy was performed under sodium pentothal and nitrous oxide anesthesia.

The patient's postoperative condition was quite satisfactory for the first 12 hours, after which the pulse became rapid, weak and irregular. Fluid began to appear in the lungs and her temperature rose gradually to 105 F. She died 8 hours later.

The gross specimen consisted of a kidney measuring 15 by 7 by 7 cm.; the kidney weighed 500 gm.; the capsule stripped with ease, was thick, white and measured 3 mm. The external surface of the kidney was coarsely nodular and smooth. Nodes measured up to 2 cm. On section the cortex and pyramids were white. Some portions of the pyramids were light tan. Cortex measured 10 mm. Pyramids measured 2 cm. The mucosa of the renal pelvis was white to purplish red. The ureter was patent; the wall was thickened.

Microscopic sections revealed small and large, poorly circumscribed areas consisting of closely arranged cords and groups of large round cells with large light staining nuclei and scanty cytoplasm. There was an occasional mitotic figure. In these areas there were few blood vessels, shrunken glomeruli and a few tubules. Tubular epithelium was markedly swollen and granular. A few of the tubules were filled with pinkish amorphous material—red blood cells.

SUMMARY

A fatal case of lymphosarcoma of the kidney, with death following operation, is presented in detail. Review of the literature and the writer's own experience point to the fact that lymphosarcoma has never been proven to be primary in the kidney. The case re-emphasizes the difficulty in making preoperative diagnosis.

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HIGH RENAL ECTOPY: A CASE REPORT

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Malpositions of the kidney are always of considerable interest to the urologist. Renal anomalies are not uncommon and have been the subject of extensive investigation. Instances of high renal ectopy are infrequent and deserve general attention.

Campbell (1930) reviewed 13,000 autopsies at Bellevue Hospital and found only 1 case of high renal ectopy. The patient died of marasmus at 1 year of age. At autopsy, there was a left diaphragmatic hernia, which admitted 4 fingers. It was plugged by the greater portion of the left kidney. An unusually high vascular supply was noted. All of the small and most of the large intestines were found in the thorax.

Eisendrath reported only 5 cases of high lumbar ectopy. In one of these, the kidney was located alongside the sac of a diaphragmatic hernia, and in another between the crura of the diaphragm.

Trauma and also eventration of the diaphragm may result in a high kidney.

All of the abdominal organs, except those fixed in the pelvis have been found in the chest. The literature regarding retroperitoneal structures in the thorax is meager. The diagnosis is often obscure and may be confused with such diverse entities as neurofibroma, pericardial cyst and diaphragmatic tumor.

The primary purpose of this paper is to report a case of high renal ectopy in which the kidney alone, in the absence of trauma, was found above the left diaphragm.

CASE REPORT

Mr. J. A., a 71 year old, married, German laborer had had 9 admissions to the Boston City Hospital and had been followed here for a variety of disorders over a period of 20 years. His urological complaints date from childhood. He was enuretic until the age of 17 and had experienced frequency, urgency and nocturia all of his life.

In November 1935, he was admitted because of intermittent, cramp-like, nonradiating pain in the left upper quadrant. He did not appear acutely ill, and the only positive physical findings were slight tenderness in the painful area and an enlarged prostate gland. Retrograde pyelograms were made, but these films have been destroyed. The radiologist's report indicated that the right kidney was normal. The left kidney was located about 6 inches above the usual position, and showed evidence of nonrotation. The left leaf of the diaphragm was thought to be elevated. Recommendations were made for fluoroscopic examination of the diaphragm and a barium meal. The patient did not wish to prolong hospitalization and the suggested studies were not performed. He was discharged with the diagnoses of 1) eventration of the diaphragm, 2) malposition of the left kidney and 3) chronic prostatitis.

He continued to complain of frequency and nocturia. Cystoscopic examination, in February 1939, demonstrated 45 cc residual urine and right lateral and middle lobe prostatic hypertrophy. Conservative therapy was instituted, but his symptoms remained unaltered.

At cystoscopy, in November 1939, the left ureteral orifice could not be visualized because of elevation of the bladder base. Pyelograms of the right kidney were made and no abnormalities were found.

In December 1940, he was hospitalized for right epididymitis, which responded to the usual treatment. For the next 4 years, he was followed in the out-patient department without improvement in his original complaints. In addition, he experienced perineal pain, hematuria and noted that his urine had a foul odor. Urinalysis showed an alkaline reaction with albuminuria and microscopic hematuria.

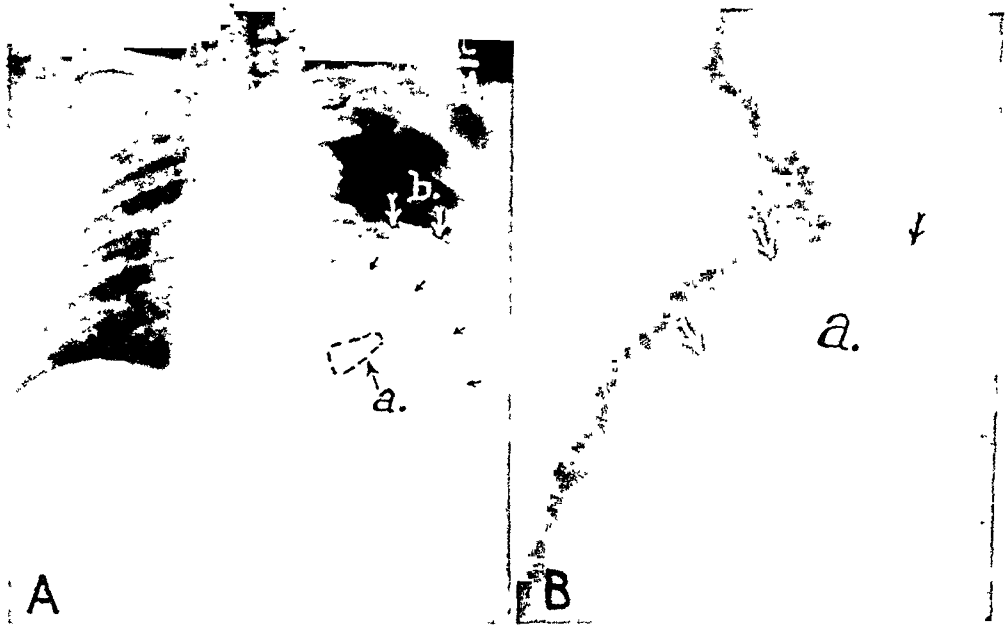

FIG. 1. *A*, faint area of calcification in left intrathoracic kidney indicated by *a*. Hypertensive type of cardiac silhouette with small arrows denoting prominent left ventricle of heart. Large arrows, *b*, show margin of intrathoracic kidney. *B*, lateral projection, showing posteriorly placed intrathoracic kidney, *a*. Note large gastric air bubble.

On November 20, 1944, he was readmitted and a 2-stage suprapubic prostatectomy was done. Bladder calculi were removed at the time of the initial cystotomy. The patient was discharged after 1 month with the clinical and pathological diagnosis of benign prostatic hypertrophy. During the next year, he was followed in the medical clinic for symptoms of coronary insufficiency and hypertension.

In April 1946, he was again examined by the urologists because of suprapubic and left testicular pain. The cystoscopist noted bladder neck fibrosis, but failed to obtain a left nephrogram on retrograde pyelography. Routine intravenous pyelograms, in November 1946, showed no change in the right kidney. The left ureter was visualized, but the left renal pelvis and calyceal system were not seen.

Cystoscopy, in June 1948, showed recurrent lateral and median lobe prostatic enlargement. On July 17, 1948, he was admitted for transurethral prostatic re-

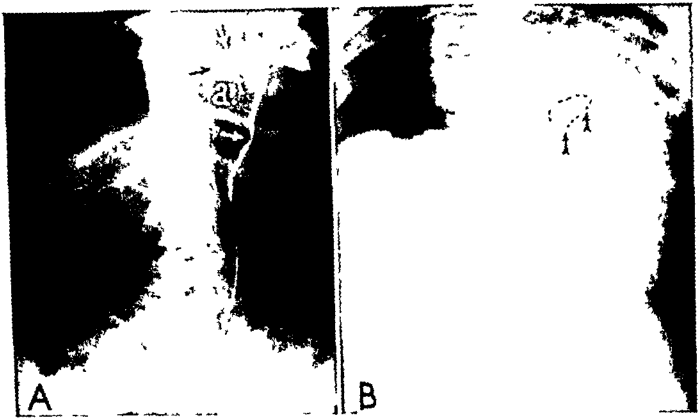

FIG. 2. *A*, calcification in or near left intrathoracic kidney indicated by *a* and upper arrows. Lower arrow suggests possible narrowing of left ureter at level of diaphragm. *B*, retrograde urogram in upright position of left intrathoracic kidney. Arrows and dotted line signify area of calcification.

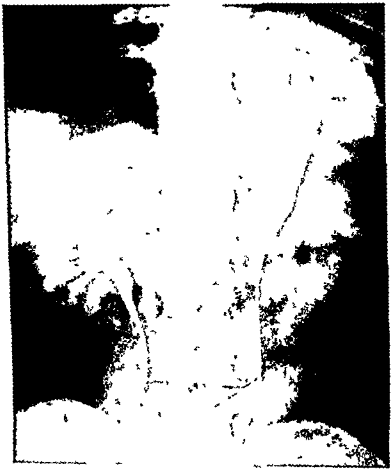

FIG. 3 Retrograde pyelogram 6 months later reveals no change in left kidney.

section. In addition to his urinary complaints, he had mild orthopnea and slight dyspnea. It was of interest that a daughter had died of pulmonary tuberculosis.

The patient was a well developed and nourished white man who appeared younger than his stated age and was in no acute distress. The only pertinent physical findings were dullness to percussion with absent breath sounds at the left lung base posteriorly and a recurrent, left inguinal hernia. Blood studies were within normal limits. Serology was negative. Urinalysis showed albuminuria 1 plus and microscopic hematuria. Roentgenograms of the chest revealed an abnormal density at the left lung base posteriorly (fig. 1). On fluoroscopy, the diaphragm was observed to move below the mass. At cystoscopy, good renal function was noted bilaterally. Left retrograde pyelograms were done (fig. 2). A progress meal showed no abnormalities of the intestinal tract other than diverticulosis. On July 21, 1948, a transurethral prostatic resection was done and 15 gm. of adenomatous tissue were removed. The patient was discharged 9 days after operation. Retrograde pyelograms 6 months later (fig. 3) show no change.

EMBRYOLOGY AND ANATOMY

The nephrogenic anlage (metanephros) in man is located far caudad in the pelvis. This secretory portion of the adult kidney is carried cranially by the ureteric bud and the downward growth of the trunk. At about the seventh week (17 mm. embryo), the entire mass lies opposite the second lumbar segment, which is the permanent position of the mesially rotated renal pelvis. The blood supply is obtained from several temporary sources, any of which may become permanent vessels. In cases of high ectopy, an abnormally high vascular derivation is usually found which suggests that the kidney is elevated by its high aortic attachments.

The diaphragm is derived from four main sources: a) the ventral septum transversum; b) the lateral pleuro-peritoneal membrane; c) derivatives from the body wall, and d) a median dorsal portion contributed by the dorsal mesentery. The formation of the diaphragm is a complex process which is completed about the second month (20 mm. embryo). There is much variation in the degree of fusion in the muscular portion of the diaphragm. Faulty development of the pleuroperitoneal membrane results in a persistent hiatus or foramen of Bochdalek. Normally, this layer of tissue is less elastic and more easily torn than the neighboring muscle. Perhaps, the reason that it is not more frequently the site of hernia is because the area is protected by the liver and the fatty tissue surrounding the adrenal gland and the upper pole of the kidney.

In order to explain a supradiaphragmatic kidney on an embryological basis, we are forced to hypothecate not only a high vascular origin, but also retroperitoneal herniation through the left pleuroperitoneal hiatus, which later closed sufficiently to incarcerate the kidney and prevented further herniation of other organs.

COMMENT

An induced pneumothorax would have been desirable in this case to rule out conclusively eventration of the diaphragm and the conventional type of diaphragmatic hernia. Arteriography might have contributed important information as to the origin of the renal blood supply. Neither procedure was deemed advisable.

CONCLUSIONS AND SUMMARY

The literature has been briefly reviewed There are three requisites which should be fulfilled before the diagnosis of renal ectopy is irrevocably made, namely, abnormal ureteral length, malrotation of the kidney and an anomalous blood supply. The case under consideration satisfies the first two requirements; it was not practicable to attempt to demonstrate the third An effort has been made to interpret our findings from the standpoint of embryology.

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VOLUNTARY FLUID INTAKE AFTER NEPHRECTOMY[1]

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This laboratory has been interested for some time in the mechanism of death in acute anuria and in the development of methods for prolonging the duration of life of bilaterally nephrectomized animals.[2, 3] It was observed in these studies that dogs dying after 100 to 200 hours of total anuria were severely dehydrated, with plasma proteins rising from a normal of 6 gm. per cent to as much as 9 gm. per cent. This finding suggested that the proper administration of fluids might counteract some of the deleterious effects of anuria and further prolong the life of nephrectomized animals.

TABLE 1. *The fluid intake in cc/100 gm. body weight of rat per day and the survival time in hours for the various groups studied. Each figure is the average of data obtained on 7 rats*

TYPE OF FLUID INTAKE	PREOPERATIVE CONTROL	AVERAGE DAILY FLUID INTAKE, CC/100 GM. OF RATS				SURVIVAL TIME
		Unilateral nephrectomy		Bilateral nephrectomy		
		1st	2nd	1st	2nd	
						hours
Normal saline	7	11	7	10	2	81
Water	2	3	4	3	0	92
10% sucrose	43	36	41	12	2	81
Multiple selection group; fluid intake is sucrose primarily	53	54	61	12	2	61
No fluids permitted	0	0	0	0	0	84

This was tested in experiments on 8 dogs and 12 rabbits in which fluids were administered at a rate of 50 cc/kg./day of either saline or 5 per cent glucose in water or in saline. These did not significantly affect the duration of life. Postmortem examination demonstrated the tissues of these animals to be edematous.

In an effort to avoid this overhydration we decided to permit bilaterally nephrectomized animals to select certain fluids *ad libitum* in an attempt to gain some clues as to the possible fluid requirements of such animals. However, this could not be done with the uremic dog since the ingestion of fluids led to continuous vomiting and loss of chlorides. The rabbit was unsatisfactory because it does not normally drink water but depends for its water on the fluid content of its solid foods. The rat was used since it has been studied intensively for its ability to self select foods and fluids in normal and stressful situations.[4]

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[1] This department is supported in part by Michael Reese Research Foundation. Aided by the Emil and Fanny Wedeles Fund for Cardiovascular Research.

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Seventy mature albino rats of both sexes were divided into 5 groups of 14 animals each. The animals were permitted to take fluid from graduated receptacles containing either 1) tap water, 2) 0.9 per cent saline, or 3) 10 per cent sucrose in water. A fourth group was permitted a choice of all three solutions. The fifth group was given no fluids of any kind. All animals were fed with dog biscuits *ad libitum*, but were starved 24 hours preoperatively.

All animals were observed for a control period of at least 10 days during which the quantity and type of fluid intake were recorded daily. The animals were then nephrectomized in either a 1 stage operation or in 2 stages with a lapse of 10 days between removal of the 2 kidneys. Ether inhalation or intraperitoneal evipal anesthesia was used.

During the control period before surgery marked preference was shown for the sucrose solution (table 1). A greater volume of fluid was consumed by these animals than by those limited to either saline or water alone. After unilateral nephrectomy, the intake of the several fluids was not significantly affected. Activity was slightly reduced during the first 24 hours after unilateral nephrectomy but was normal thereafter.

The animals anesthetized with ether had a shorter duration of life after bilateral nephrectomy (average 50 hours) than did those anesthetized with intraperitoneal evipal. For this reason, the data on only the evipal-anesthetized animals are presented in table 1, although the results in both groups (ether or evipal) were similar with regards to fluid intake.

During the first 24 hours after removal of the second kidney the sameamount of water or saline was ingested as during similar preoperative periods. However, those animals receiving the sucrose solution reduced their intake to about $\frac{1}{4}$ the preoperative intake. On the second day after bilateral nephrectomy, the intake of all fluids was markedly diminished, and this tendency progressed until the animal died. Diarrhea developed in about $\frac{1}{3}$ of the animals during the anuric period. The animals became progressively less active until death. Six to 8 hours before death, weakness was extreme, and muscular twitchings were noted.

The average duration of life after both kidneys were removed was 84 hours; the longest, 119 hours. There was no consistent difference in duration of life between the groups in which both kidneys were removed at one operation and those in which this was done in two separate operations. The type and volume of fluid taken had no effect on the average duration of life of any group. Even those animals with no access to fluids of any kind lived as long as those which were permitted the various fluids.

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PAPILLARY EPITHELIOMAS IN EACH URETER AND IN THE BLADDER

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Three theories have been advanced to explain the origin of multiple papillary neoplasms in the urinary tract. In cases in which similar neoplasms also were present in the renal pelvis, Albarran and Imbert explained the recurrence of papillary epitheliomas in the ureter and bladder on the basis of implantation. They expressed the opinion that papillary epitheliomas of the renal pelvis exfoliated tumor cells which were carried in the urinary stream and deposited as graft implants on the lining epithelium of the ureter or bladder, or both. Cabot and Allen, Kimball and Ferris, MacKenzie and Ratner, Thomas and Regnier, Scholl, Macalpine and many others have supported the concept that multiple papillary epitheliomas of the urinary tract originate from graft implants supplied by a parent tumor.

Hunt explained the multiplicity of papillary neoplasms in the urinary tract on the principle of permeation. He said that the papillary neoplasms extended along the epithelial lining of the calyces, renal pelvis, ureters and bladder.

In contrast, Ewing said that a predisposition toward papillary epitheliomas of the urinary tract is present in certain persons and that the multiplicity of these lesions is not necessarily indicative of their origin from one growth. He explained the multiplicity of these neoplasms on the basis of multicentric origin, that is, he believed that several centers produce tumor cells which appear simultaneously or at intervals and either coalesce or remain discrete. The concept of the multicentric origin of papillary neoplasms of the urinary tract is further supported by the work of Broders, McDonald and Priestley, and Fagerstrom.

The following case is reported for two reasons: first, because we believe it lends further support to the concept of the multicentric origin of multiple papillary neoplasms; and second, because of the rare occurrence of bilateral involvement of the upper part of the urinary tract by papillary neoplasms.

CASE REPORT

A man, aged 61 years, was referred to the Mayo Clinic April 8, 1948, for treatment of recurrent neoplasms of the urinary bladder. Fifteen years previously, he had noted gross hematuria for the first time. Cystoscopy had disclosed a "benign papillary tumor" of the bladder. The tumor had been fulgurated but had recurred repeatedly. Each recurrent tumor had been fulgurated. The patient had received 2 courses of roentgen therapy in 1943. Prior to June 1947, microscopic examination always had revealed "benign papillary tumors." In June 1947, however, biopsy had disclosed a papillary transitional cell epithelioma of the bladder. The patient had received another course of roentgen therapy at that time.

During the 9 months before the patient came to the clinic, he had lost 9 pounds (4.1 kg.). Urinary urgency had been present during this time; he had had to micturate every ninety minutes during the day and 4 or 5 times each night. General physical examination did not reveal any significant abnormality.

Urinalysis disclosed albuminuria, grade 2 (on the basis of 1 to 4), erythrocyturia, grade 2, and pyuria, grade 4. The erythrocyte count was 4,550,000 and the leukocyte count was 8,600 per cubic millimeter of blood respectively. The value for the hemoglobin was 12.6 gm. per 100 cc of blood. A flocculation test did not disclose any evidence of syphilis. The value for the urea was 40 mg. per 100 cc of blood, and the sedimentation rate of the erythrocytes was 10 mm. in 1 hour (Westergren's method). Roentgenographic examination of the thorax and pelvis did not reveal any abnormality. Excretory urography disclosed dilatation of the pelvis and calyces of each kidney.

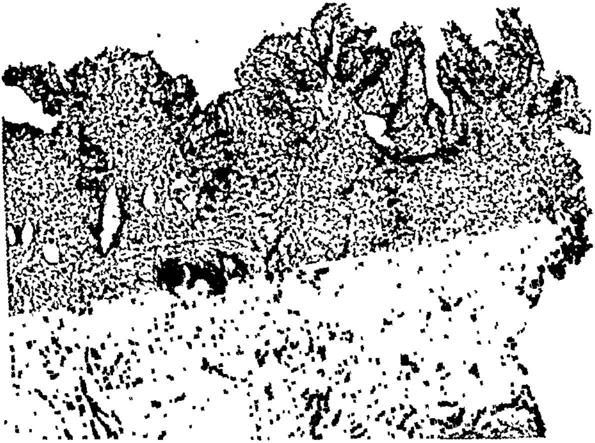

FIG. 1 [illegible]lioma, grade 2 of bladder. (Hematoxylin and eosin stai [illegible]

Cystoscopy disclosed a flat sessile tumor which had poorly defined borders and covered most of the lower half of the bladder. A specimen of tissue was removed from the bladder for biopsy. Cystoscopy also disclosed dilatation, grade 4, of the orifice of each ureter. Microscopic examination of the specimen did not disclose any evidence of malignancy, and bimanual examination of the pelvis did not reveal any perivesical infiltration. The patient's home physician was

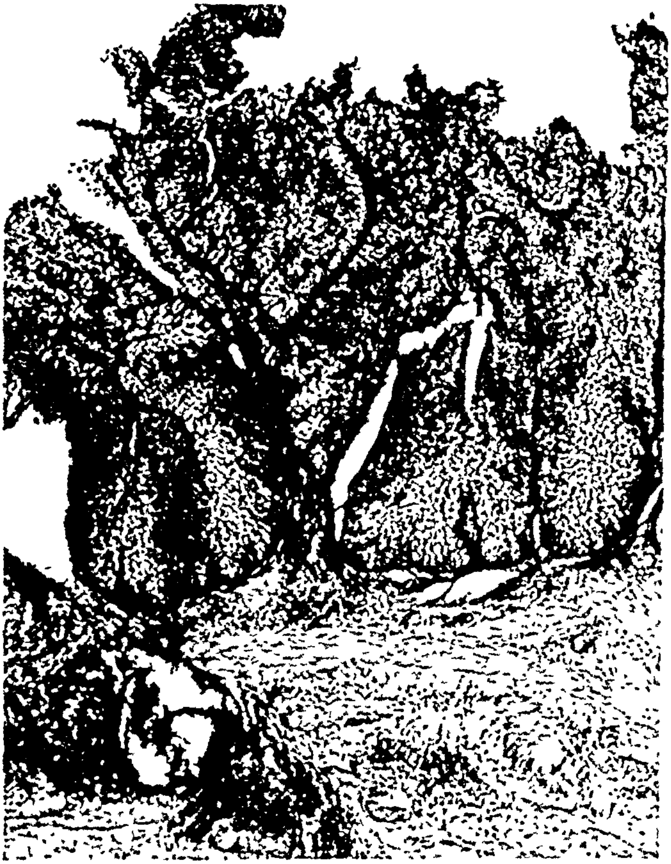

FIG. 2. Papillary transitional-cell epithelioma, grade 2, of lower portion of right ureter. (Hematoxylin and eosin stain; × 50.)

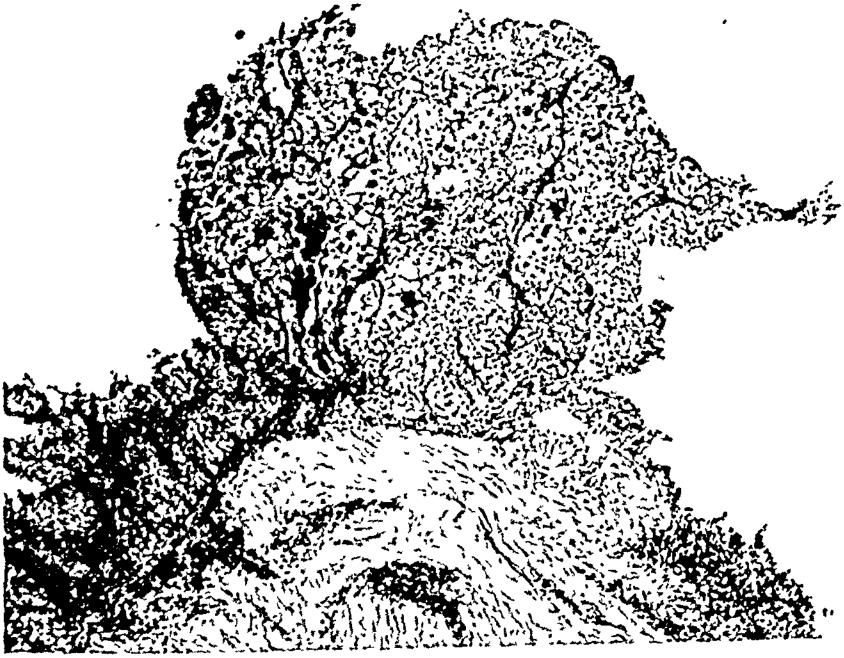

FIG. 3. Papillary transitional-cell epithelioma, grade 2, of lower portion of left ureter. (Hematoxylin and eosin stain; × 51.)

asked to send us a specimen of the tissue that had been removed for biopsy in June 1947. Microscopic examination of this specimen by Dr. J. R. McDonald of the Section on Surgical Pathology confirmed the diagnosis of papillary epithelioma, grade 2.

Operation did not reveal any evidence of extension of the tumor into the perivesical tissues. Total cystectomy was performed. Since the lower portion of each ureter was 1 cm. in diameter and was the site of considerable thickening and induration, a portion of each ureter was removed with the bladder. Bilateral cutaneous ureterostomy then was performed.

Gross examination of the surgical specimen revealed a tumor of the base of the bladder and a papillary neoplasm in the intramural portion of each ureter. The intervening mucosa appeared to be normal. Microscopic examination disclosed multiple papillary transitional-cell epitheliomas, grade 2 (Broders' method), of the bladder (fig. 1) and a similar tumor in the lower portion of each ureter (figs. 2 and 3). The tumors of the ureter were distinct from those of the bladder. There was no evidence of infiltration of muscle.

The convalescence was uneventful. On the third day after the operation, chemical analysis revealed the following values: urea, 28 mg. per 100 cc of blood; chlorides, 538 mg. per 100 cc of plasma; carbon dioxide combining power, 50 volumes per 100 cc of plasma. On 2 occasions, microscopic examination did not reveal any malignant cells in urine collected from each ureteral stoma.

COMMENT

It does not appear probable that epithelial cells which have been exfoliated from a parent tumor and have been bathed in urine can become embedded and grow on an intact epithelium. In the case which we have reported, it does not appear probable that tumor cells which were exfoliated from the vesical neoplasm became embedded and grew on an intact ureteral epithelium as a result of reflux up each ureter.

This case led us to make a study of 147 cases of tumor of the renal pelvis in which the patients were observed at the clinic in a period of 37 years, namely, January 1, 1910 to December 31, 1946, inclusive. In 5 of the cases, a tumor of the bladder had preceded the appearance of a tumor in the renal pelvis. In 24 cases, a vesical tumor developed after nephro-ureterectomy had been performed to remove a tumor of the renal pelvis. In these cases, cystoscopy did not disclose any evidence of a vesical tumor at the time of nephro-ureterectomy. These findings would be difficult to explain on the basis of implantation.

Broders pointed out that in the majority of cases of multiple and recurrent tumors of the urinary tract the uniformity of the histologic changes can be compared with that of adenomas or polyps of the large intestine. When these polyps undergo carcinomatous transformation, they are independent of each other and present a uniform histopathologic picture. Broders also said that papillary growths of the renal pelvis, ureter and bladder show a definite continuity with the basal cells of the mucosa and that this indicates that the tumors originate in these cells. McDonald and Priestley made a histologic study of 75 cases of tumor of the renal pelvis and found that the highest incidence of carcinoma of the corresponding ureter and the bladder occurred in cases in which the tumor was of the noninfiltrative type. Presman and Ehrlich said that metastatic lesions of the ureter involve all of the layers of this structure except the mucosa. The noninfiltrative character of multiple papillary neoplasms suggests that they arise from the basal cells of the mucosa rather than by metastasis by way of the lymphatics. The presence of normal intervening mucosa between the multiple papillary epitheliomas would tend to deny the possibility of spread by permeation.

The presence of bilateral papillary epitheliomas in the urinary tract is rare. Murchison, in 1870, reported a case of bilateral villous processes in the renal pelvis and the presence of villous processes surrounding each ureteral orifice. A review of the literature disclosed 5 similar cases. Maybury and Dyke, Retzlaff, and Sanford each reported a case of papillary epithelioma of each renal pelvis. Macalpine recently reported 2 cases of bilateral renal papillomas in which the patients were dye workers. In the 147 cases of tumors of the renal pelvis observed at the clinic, there were no cases of bilateral papillary neoplasms. Bilateral papillary neoplasms are not frequently encountered. Their presence can best be explained by the concept of multicentric origin.

SUMMARY

This report is based on a case in which a papillary epithelioma was present in each ureter and in the bladder. A better understanding of the origin of papillary epitheliomas of the urinary tract is necessary for a planned and effective method of treatment. The destruction or removal of a papillary epithelioma of the urinary tract does not eliminate the predisposition for similar growths to recur. Persistent and frequent surveys of the urinary tract are imperative in cases in which a papillary neoplasm has been found if the so-called recurrent lesions are to be found and destroyed early. Papillary growths in each ureter and in the bladder can best be described as multicentric epitheliomas. The destruction or removal of multicentric epitheliomas does not eliminate the predisposition for similar growths to recur.

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A NEW METHOD OF URETEROSIGMOIDOSTOMY[1]

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In 1936, Hinman was able to find over 60 reported techniques for uretero-intestinal transplantation recorded by over 50 different surgeons. Since that time many new techniques have been reported, which on careful study are found to be modifications or slight changes of previous operations. The very great number of modifications indicates that the ideal operation has yet to be achieved. The operation to be described is also a modification and while it is not ideal, it has given the best results of any technique used thus far by me.

A brief historical review is of interest since it points out the problems involved which we have yet to settle. Simon, in 1851, attempted to produce a urinary-fecal fistula by means of sutures between the ureters and the rectum which was successful in producing the fistula, but unsuccessful as to end result. In 1930, Kirwin experimentally showed that the idea of a long fistula was unsound and that it led to stricture of the fistula due to the failure of epithelization.

The first recorded operation of uretero-intestinal anastomosis was that by Smith in 1878, and unfortunately was unsuccessful. Maydl, in 1894, introduced the idea of implanting the entire trigone with the intact ureters in cases of exstrophy of the bladder, hoping to preserve the sphincteric action. Bergenhem later published successful cases using an extraperitoneal incision and implanting a rosette of bladder tissue with each ureteral orifice. Peters, independently, a short time later reported on a method quite similar to Bergenhem, but added the factor of retained ureteral catheters. Fisher, in 1938, reported a patient surviving 22 years after a Peters' type of transplantation.

The idea of mechanical aids to the operation was first proposed by Chalot in 1896, and he used hollow nickel tubes to hold the ureter open and pass into the rectum. This idea finds its modern counterpart in the experimental use of vitallium tubes by Stevens and Lord.

In 1896, Fowler attempted to produce a valve-like action by using a flap of rectal mucosa. Falk and Smith have reported a case surviving 25 years after Fowler's operation. The recent work of Davalos, first with dogs, and later with human beings, is really a modification of Fowler's original technique.

In 1886, with an idea of preventing leakage, Bardenheuer experimentally buried the ureter into the bowel wall after the fashion of a Witzel gastrostomy. In 1887 he applied this idea to a human case. In 1905, Tikhoff also proposed the same idea. Their method was further modified by Mirotvortzeff, who in addition to burying the ureters, also sutured the ureteral mucosa to the intestinal mucosa (after Shilovtzeff). This was also proposed by Stiles in 1907. Its modern counterpart is Riba's experimental study in 1939.

Coffey, in 1911, introduced the idea of submucosal implantation with his

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[1] Read at annual meeting, South Central Section, American Urological Association, St. Louis, Mo., October 27, 1948.

Coffey I operation. This has been modified innumerable times. Mayo, in 1912, introduced a piece of catgut up the ureter to act as a guide and prevent postoperative anuria. This became widely known as the Coffey-Mayo technique. In 1921, Cabot used the extraperitoneal approach in doing the Coffey I operation. Today, of course, it is well known that peritonitis is due to leakage and not to contamination. The widespread use of sulfa drugs and biologics to control contamination make the avenue of approach of much less importance than formerly. Exposure is so much better transperitoneally that it is more widely used. It also permits implanting both ureters through the same incision and at the same time, if desired. Lower also modified Coffey's technique by splitting the end of the ureter to produce a wider lumen. Beck, in 1913, produced an internal tunnel with the free end of the ureter dangled in the lumen of the gut. In 1928, Marion also tunneled the bowel wall between two separate incisions. Mayo, 1930, proposed the idea of tunneling the muscularis of the bowel between several incisions. Walker-Taylor, 1931, experimentally guided the ureter, attached to a long needle, through the muscularis and into the lumen of the intestine. Schinagel, 1948, also reports on the experimental use of the tunneling idea.

Coffey next introduced his technique II. At this time he introduced the idea of postoperative drainage by means of a retained catheter. This, of course, basically is the same idea proposed by Mayo with the catgut guide. Coffey's third technique was then proposed with the addition of a cutting or necrosing stitch to make the anastomosis between the ureter and intestine after ligation of the ureter. The disadvantages of the third technique are immediately apparent, for until the suture can produce necrosis of the ureter and intestine, there will be no urinary output.

In 1933, Higgins allowed the ureter to remain connected with the bladder during the time that the necrosing suture took to cut through, thus protecting renal function by allowing for drainage. Hinman, in 1935, reported on the use of drainage by means of an extraperitoneal ureteral catheter, but did not recommend it because the catheter caused necrosis and infection in a clinical case. Vose, 1945, used a T-tube ureterostomy to relieve the edema that follows ureteral transplantation, and had no complications in his series of cases. In 1948, Flocks left the ureter intact, opened a side to side anastomosis between ureter and bowel which he maintained open by a retained ureteral catheter passed out the bowel and through the anus. In these methods the ureters are tied off at the second stage with the exception of Flocks, who places a wire suture around the ureter at the first operation and later ligates the ureter by twisting the suture down. Vose, of course, first clamps off the T-tube and later pulls it out.

A number of other mechanical aids have been proposed, many of them being modifications of previous instruments. Ferguson, in 1931, implanted the intact ureter first, and then at a second operation severed the ureter where it emerged from the gut, opened the ureter into the bowel with an electrode passed up the ureter, fed a short catheter up the ureter and then out the bowel. Poth, in 1935, placed the intact ureter in the bowel wall, then at a second operation cut the ureter, passed a special electrode into the ureter and out the lumen of the gut where it was removed by an assistant with a proctoscope and cautery. In 1944, Jewett published his modified technique using an electrode of different design, but in the same way that Ferguson had proposed. Jewett did not use ureteral catheters. Hinman, in 1936, ligated the ureter around a special "divisible carrier" and introduced it into the lumen of the gut where the carrier could be manipulated to cut the suture, opening the ureter and leaving the portion of the carrier which was contaminated inside the lumen of the gut.

While its popularity varies widely from region to region, and even from time to time in the same region, uretero-intestinal transplantation fills a definite need. While the mortality leaves much to be desired, and even at times is terrific, its morbidity over cutaneous implant cannot be questioned. In defense of the procedure, it must be stated that some of its mortality is unquestionably due to the fact that it has been reserved as a "last chance" therapy when all other means of treatment have failed. Enough reports of long time survivals have now accumulated to show that it is a feasible procedure. (Stevens 1941, Priestley and Strom 1943, McComb and Pearse 1943, Lower 1943, Marshall and Gardner 1945, Smith 1947, and Vallett 1947.)

A great deal of experimental work has been done on the problem (Hinman, Belt, Weyrauch, Fortner, Kiefer, Vermooten, Spies and Newswanger) and in addition, Hinman and Weyrauch have studied the different principles of surgery which have been used, in an attempt to find the causes of the difficulties. The difficulties are well known and familiar to all. They are: 1) danger of peritonitis; 2) danger of urinary obstruction; 3) danger of urinary infection. The causes of them are not well known. Modern drugs and biologicals have led, together with the introduction by Coffey of the submucosal implantation, to almost conquering the dangers of leakage and peritonitis. The problems of urinary obstruction and infection are still with us.

Hinman and Belt, working with dogs, found that while the duodenum, by virtue of its sterility, would be an ideal place to insert the ureters, the absorption of waste products led to similar death as that following nephrectomy. This has been confirmed recently by Fortner and Kiefer using monkeys as experimental animals. Thus one is limited to using the large bowel or at least only this plus the terminal ileum. Vermooten has done experimental transplants in dogs into the terminal ileum with the idea of being aided by the ileo-cecal valve, but was not impressed by any particular value of this procedure.

Hinman and Weyrauch studied the causes of peritonitis following transplantation and found it due to: 1) leakage because of imperfect closure; 2) sutures perforated bowel or ureter; 3) one or more sutures at site tore out; 4) local necrosis of bowel or ureter due to interference with the blood supply. Flocks believes that interference with blood supply is all important and in experimental studies has shown that any section of the ureter is supplied from above and below. The cut end of any ureter will, therefore, slough to some extent. Hinman and Weyrauch have produced additional experimental work in chickens to show first, that chickens, even though they have a cloaca, are susceptible to urinary obstruction and infection; and secondly, when the ureter is re-anastomosed to the cloaca, obstruction of the ureters and infection are incident to changes produced at operation.

Vermooten attempted to solve the problem by first re-implanting the ureters into the bladders of dogs. In this case he found that obstruction occurs when the lower end of the ureter retracts within the wall of the bladder. Vermooten next did uretero-intestinal transplants and found that the ureteral bud within the rectal lumen was always the site of suppuration, but came to the conclusion that the ureter must be fixed so that it cannot retract. He also proved that if ureteral catheters are left in a ureter whose stump is placed inside the intestinal lumen, that part of the ureter within the lumen will come away when the catheter is withdrawn. Vermooten's ultimate conclusion was that infection at the site of the bed of the transplant produced stricture formation. This view more recently has been expressed by Jewett. In a third series of experiments, Vermooten has also shown that the so called "ureterorectal valve" produced by submucosal implantation does not function as a valve, but that even an incompetent valve does not always necessarily lead to ureteral dilatation.

After a period of dog and autopsy experiments, my first uretero-intestinal transplants were done with the Coffey I type of operation, and then with Lower's method. One of the first of these is now living and well after 6 years. None have survived without marked renal dilatation. Use of the Coffey II operation was uniformly disappointing. Use of Higgins' technique was abandoned because of frequent postoperative anuria, even though the ureter was still connected with the bladder. Jewett's technique produced excellent results in several patients one of whom is now living over 3 years with a single kidney, and no evidence of hydronephrosis or impairment of renal function. In several other cases, however, distressing fistulas were produced by tangential cuts, and as there seemed no sure technical way of avoiding this distressing accident, this method was also abandoned. In trying to develop a new technique it seemed that several requirements must be met: 1) The submucosal trough, while it furnishes an imcompetent valve, does prevent leakage and should be used. 2) If the ureteral stump does become infected inside the gut lumen, it should be kept outside the lumen. 3) If the cut end of the ureter does slough, it should not be utilized directly in the formation of the anastomosis. 4) No sutures should be placed in the ureter or gut lumen where there is any danger of inadvertently perforating either structure. 5) Some provision should be made for drainage immediately postoperatively. 6) The procedure should be accomplished immediately under direct vision. These requirements, of course, indicate that a lateral anastomosis would have to be done. With the above objectives in mind the following technique was worked out first on dogs, and then on human beings.

OPERATIVE TECHNIQUE

A midline incision is made from the symphysis to, or around, the umbilicus. The intestines are packed off from the pelvis and a self-retaining retractor is inserted. The posterior peritoneum is incised over the right ureter and the ureter identified and freed down toward the bladder (fig. 1, *A*). The ureter is then clamped, cut, and the distal end ligated. The sigmoid is pulled over and the site selected for the transplant is marked off with stay sutures through the muscularis. The usual submucosal trough is prepared by separating the muscularis of the sigmoid from the mucosa for a distance of about 2 cm. The clamped ureter is then held over the prepared bed and ligated at the level of the lower end of the trough with No. 40 cotton and the ends of the ligature then left long (fig. 1 *B*).

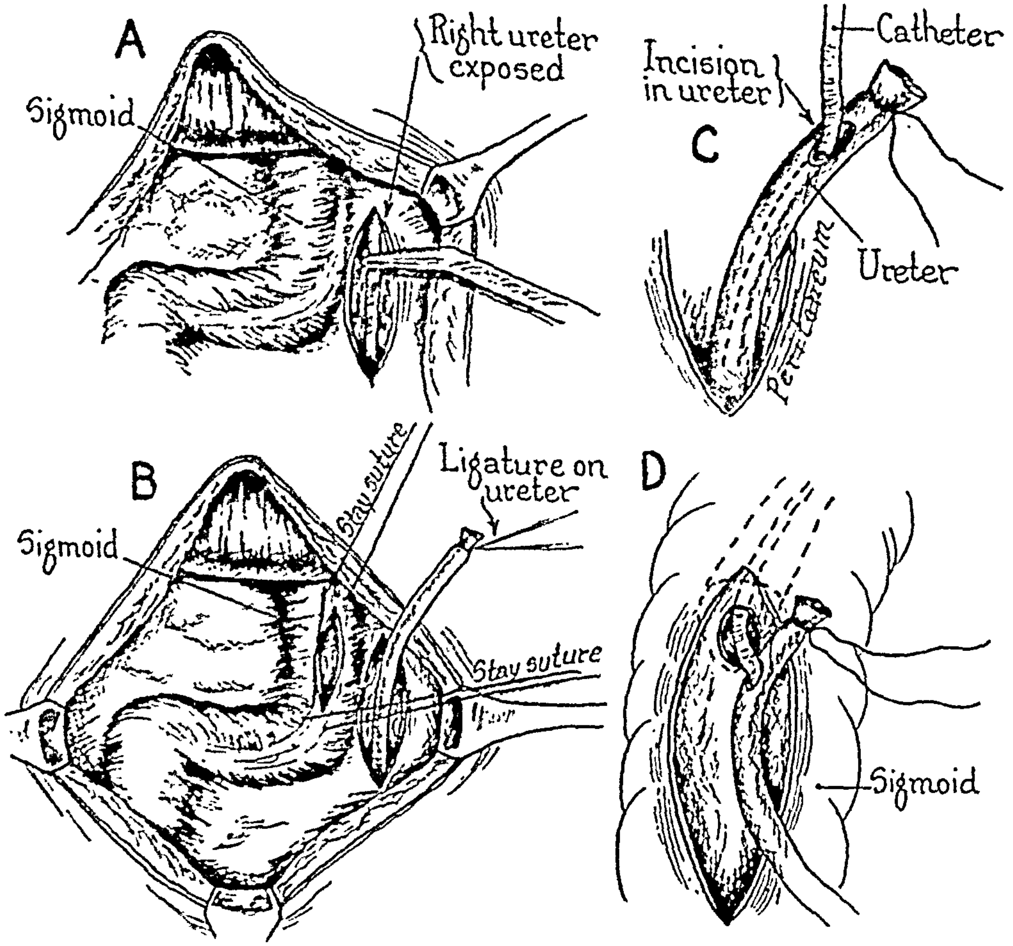

Fig. 1. *A*, sigmoid freed, incision made in posterior peritoneum, and ureter exposed. *B*, submucosal trough made in sigmoid. *C*, incision in ureter behind ligature; catheter inserted up ureter. *D*, stab wound made in sigmoidal mucosa over tip of rectal tube; distal end of catheter passed through tube to outside.

A ureteral catheter or Suby tube is then inserted up the ureter through a longitudinal incision in the ureter about 1.5 cm. behind the ligated end (fig. 1, *C*). The excess ureter beyond the ligature is removed. The ureter is then placed in the prepared bed and the muscularis of the sigmoid closed over the upper end of the bed. A 34F whistle tip rectal tube, or the special catheter designed by Flocks, is then introduced through the rectum and manipulated so that the eye lies under the incision in the ureter. A stab wound is then made in the lumen of the sigmoid and the distal end of the catheter is threaded down the rectal tube until an assistant can grasp it, after which the rectal tube is withdrawn, leaving the ureteral catheter in place (fig. 1, *D*). The ends of the ligature on the end of the ureter are then threaded on needles and a mattress suture placed at the lower end of the bed and tied on the surface of the sigmoid. The remainder of the muscularis is then closed over the ureter (fig. 2, *A* and *B*). In the last 2 cases, in addition to the above, the mucosa of the ureter is sewn to the mucosa of the sigmoid. This should be a safety precaution in case the ureteral catheters are accidentally removed. The lateral portions of the posterior peritoneal flap are then utilized to immobilize the sigmoid at the point where the ureter enters the new sigmoidal bed, to prevent kinking (fig. 2, *C*). The same procedure is carried out on the other side. Figure 2, *D* shows the completed anastomosis.

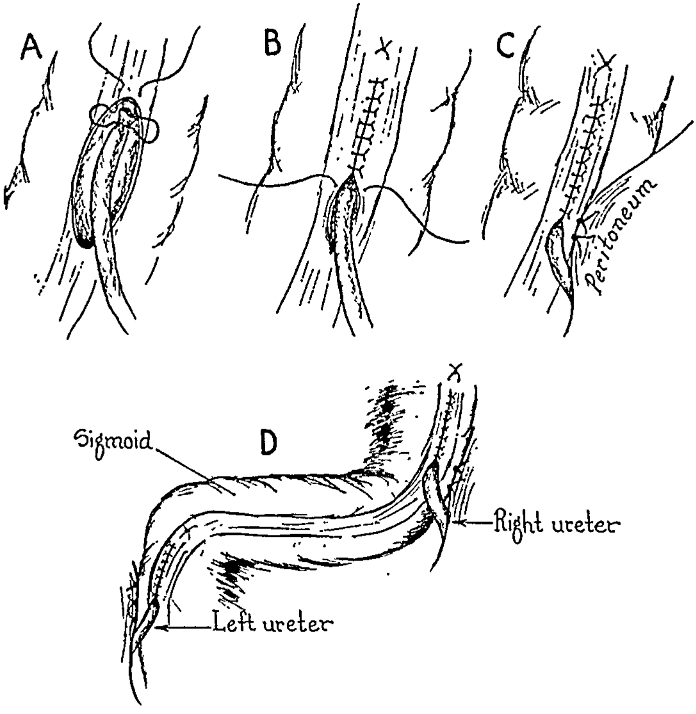

FIG. 2. *A*, end of ureter is pulled up under distal end of submucosal trough. *B*, rest of bed in sigmoid is closed over ureter. *C*, lateral edge of posterior peritoneal flap is fixed to sigmoid to prevent kinking of ureter. *D*, completed anastomosis.

No attempt is made to extraperitonealize completely the entire area of anastomosis because this may kink the ureters and may also cause some intestinal obstruction. In regard to infection, the use of sulfasuxidine, sulfathiazole,

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RECURRENT TRAUMATIC INTRAPERITONEAL RUPTURE OF THE BLADDER

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Many cases of rupture of the urinary bladder have been reported, but a review of the literature reveals only 3 cases of recurrent, nontraumatic rupture. Marbury and Fry reported a case in which alcohol and lues played an etiological role in the ruptures. Pole's case was due to gonorrheal strictures and multiple bladder and perineal operations. Oppenheimer and Druckerman added another case in which bladder infection and obstruction at the vesical neck predisposed to the the spontaneous rupture on two occasions in the same patient. All the above cases recovered following surgical intervention. Because of the rarity of the condition and the peculiarities presented, a case is herewith reported of a recurrent rupture of the bladder, which to the minds of most critical clinicians would have to be considered as one due to trauma.

CASE REPORT

N. P., a white laborer aged 50, was admitted to the hospital on September 1, 1947, complaining of diffuse abdominal pain, which had begun 8 hours previously with an acute onset. Micturition was normal until a few hours before the onset of pain, and from that time on he had an urgent desire to void but was unable to do so. No history of trauma was obtained and he stated he consumed only 3 glasses of wine previous to the onset of his symptoms. He was repeatedly questioned about trauma and alcohol but he never deviated from his original story. No other symptoms were present.

Physical examination revealed a well nourished, well developed man in acute distress with severe abdominal pain, but not in shock. Exquisite tenderness and marked rigidity were present throughout the abdomen. Distention was not present and peristalsis was diminished. No shifting dullness was obtained. Rectal examination was normal.

Temperature was 98 F, pulse 96, respirations 22, and blood pressure 130/90. White blood cell count was 14,400 with 87 per cent polymorphonuclears and 13 per cent lymphocytes. Red blood cell count was 4,200,000, with 13 gm. hemoglobin. Blood chemistry was normal. Kahn test negative.

Catheterization of the bladder recovered 500 cc of deep red bloody fluid. Sterile saline (50 cc) was injected into the bladder and 75 cc of blood-tinged solution returned. This was repeated with the same results.

Soon after admission the blood pressure rose to 144/100 and the pulse increased to 140 with a temperature of 102 F. An intravenous urogram revealed a normal upper urinary tract and a cystogram showed the ruptured bladder with intraperitoneal extravasation of dye (fig. 1, *A*).

Immediate surgical exploration was performed. The bladder was opened and on the left superior wall was a ragged tear, 5 by 3 cm., extending into the peritoneal cavity. No active bleeding points were found but many clots were evacuated from the peritoneal cavity through the rent in the bladder. The peritoneum was then opened and many more clots were removed. Approximately 200 cc bloody fluid was also aspirated from the peritoneal cavity. On the right lateral wall of the bladder there was a 7 cm. tear of the peritoneal reflection of the bladder. This rent in the peritoneum did not communicate with the bladder cavity but extended into the perivesical space. The bowel was normal.

The hole in the superior wall was sutured with continuous chromic catgut on the peritoneal side of the bladder. The tear of the peritoneal reflection was sutured in a similar manner and the peritoneum closed without drainage. A cystotomy tube was placed in the bladder and a Penrose drain placed down to the peritoneum, following which the wound was closed in the usual manner.

The postoperative course was marked by abdominal distension which was finally controlled by a Wangensteen tube, eserine and strychnine. Chemotherapy and intravenous fluids were started. The Wangensteen was removed on the sixth day and the remainder of the stay in the hospital was uneventful. He was discharged 3 weeks after surgery in good condition, without complaints.

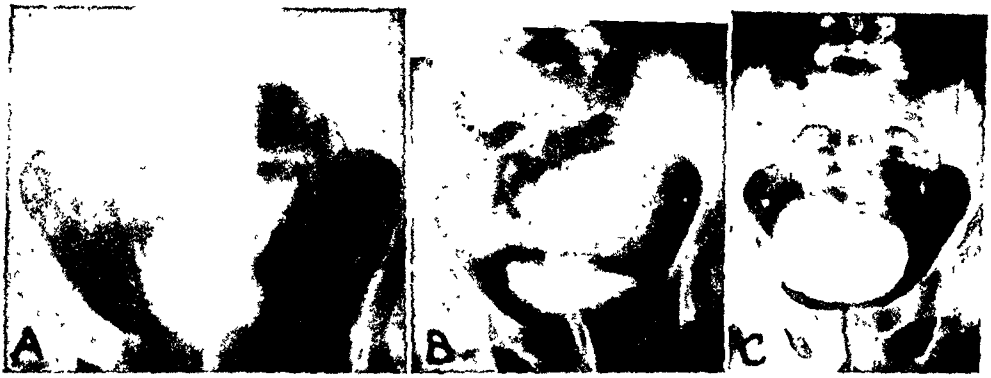

FIG. 1. A, cystogram, showing tear in superior wall of bladder and intraperitoneal extravasation of dye. B, cystogram showing second intraperitoneal rupture in the same patient 4 months later. Dye localized in peritoneal cavity. C, cystogram, normal, 3 weeks after repair of ruptured bladder.

The patient was not seen again until readmitted to the hospital on January 26, 1948, four months after discharge. He complained of generalized abdominal pain and urinary retention for 24 hours. He stated the day before this admission he slipped on the icy pavement and fell to the ground. Following this accident the above symptoms began. He had vomited 3 times since the onset. At this time he was again questioned about any traumatic cause of his initial rupture 4 months previously, and without hesitation he stated that while pushing a wheelbarrow he tripped, fell and the handle of the wheelbarrow struck his abdomen.

On examination, exquisite tenderness and slight rigidity were present in both lower quadrants of the abdomen. Peritoneal rebound tenderness was also elicited in this area. The temperature was 100 F, the pulse 98, respirations 22, and the blood pressure 180/110. The white blood cell count was 15,700 with 81 per cent polymorphonuclears and 19 per cent lymphocytes. The red blood cell count was 4,500,000 with 14 gm. hemoglobin. Urea nitrogen 16. Kahn test negative.

A catheter was easily passed into the bladder and 100 cc. clear, amber urine was obtained. A cystogram revealed extravasation of the Diodrast (fig. 1,*B*) and immediate surgical exploration was carried out.

The previous scar was excised and many dense fibrous adhesions were present around the bladder. The bladder was opened and 150 cc of amber urine was aspirated. On the left superior wall, at the site of the previous rupture, there was a hole in the bladder, 1 by 1 cm. The edges of the tear were thickened and fibrous, and pressure on the abdomen caused urine to exude from the peritoneal cavity into the bladder through the tear. The rent was closed by a pursestring suture taken around the edges in the bladder. The peritoneum was then opened and about 200 cc of cloudy urine was removed. There appeared to be a partially encysted portion of the peritoneal cavity surrounded by adhesions and fixed to the bladder by scars of previous accident. It was felt, since this cavity was partially separated from the general peritoneal cavity, that drainage should be instituted; therefore, a Penrose drain was inserted in this cavity (fig. 1, *B*), the peritoneum closed, and the wound sutured in the usual manner.

The patient made an uneventful recovery. He was up on the second day, the Penrose drain removed on the sixth day, and he left on the twenty-third day completely well. An intravenous urogram, taken before discharge, showed a normal upper urinary tract. A cystogram revealed a normal bladder (fig. 1, *C*).

COMMENT

The causes, diagnostic maneuvers, and treatment of bladder rupture have frequently been discussed in the literature. However, the intraperitoneal type of rupture usually follows a characteristic course although it could simulate and must be differentiated from any condition causing an acute surgical abdomen. There is usually a history of some difficulty in voiding, urgency, or passing of small amounts of blood-tinged urine before the onset of abdominal complaints. The abdominal pain is usually severe, with a sudden onset, which may not be well localized by the patient. The patient may be in shock, mild or severe, depending upon the time that has elapsed from the onset of symptoms. The abdomen is rigid and tender. Fullness in the flanks will depend upon the amount of free urine and the intensity of the peritonitis, which may be either chemical, bacteriological, or both, depending upon whether the urine at the time of rupture was infected or not. Peristalis is diminished. Rectal examination may reveal a bogginess in the cul-de-sac just above the prostate.

Methods of diagnosis that have been advocated at various times include vesical pneumograms, injection of radiopaque substances into the bladder, cystoscopy and catheterization. A measured amount of sterile saline is injected into the bladder through a catheter and if a lesser amount returns, it indicates a ruptured bladder. However, in our case more fluid returned than was injected which would suggest an intraperitoneal rupture since it would be assumed that some of the fluid was obtained from the intraperitoneal extravasation.

During our patient's initial hospitalization, he steadfastly denied any history of trauma whatsoever, nor did he ever deviate from his story of having drunk only three glasses of wine the day previous to admission. We thought, perhaps, extrinsic etiological factors were eliminated. During his second stay in the hospital he stated that 12 hours previous to his first admission the handle of a wheelbarrow struck him in the abdomen. Thus, were it not for his second ruptured bladder, this case would have been considered one due to internal causes or spontaneous. When the criteria of spontaneous rupture depend upon the history of external stimuli, it is quite likely that many patients may forget a slight jar or fall, just as this patient did. Campbell stated that trauma may be no more than exertion of getting out of bed, straining at stool or a slight fall. In those ruptures due to a fall, the distance fallen is unimportant.

CONCLUSIONS

A case of recurrent, traumatic, intraperitoneal rupture of the bladder with recovery is presented. The diagnosis and symptoms are briefly discussed. When the criteria of spontaneous rupture of the bladder depend upon the history of the patient, in many cases it is inaccurate, as shown in the case presented.

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ENDOMETRIOSIS OF THE BLADDER[1]

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Endometriosis involves the urinary tract rather rarely. The bladder is most commonly affected, but according to the latest review only 64 cases of endometriosis of the bladder have been reported in the literature.[2] Another case is herein reported.

The term endometriosis, along with various other terms, is used to denote an aggregation of ectopic or misplaced endometrial glands with stroma found in organs or locations other than the uterus. The condition has been reported in the labia, the perineum, the inguinal lymph nodes, the uterus, the urethra and the bladder as well as the more commonly involved pelvic viscera. The disease is limited to women of the menstrual years.

The mode of origin in these extraneous locations is an unsettled question. Theories advanced include: 1) Primitive cell "rest" of the wolffian or müllerian ducts; 2) metaplasia; 3) invasion or direct extension or metastasis resulting from surgical trauma or pelvic disease. These growths have also been academically classified as internal or external, and primary or secondary, depending upon their possible mode of origin or their location in relation to the organ involved or their relation to the adjacent pelvic organs. No theory of origin or classification yet expounded will satisfactorily fit all the cases so far reported. The weight of opinion seems to favor direct extension or invasion. Some authors are very emphatic on this point. There is no disagreement, however, on the basic fact that these tissue masses are under direct hormonal influence, especially the ovary, and that the symptoms and manifestations are "cyclic" in character. In endometriosis of the bladder therefore, the symptoms will be exaggerated during periods of menstruation. Bladder pain, frequency and urgency are the chief symptoms. Hematuria will occur only in cases where the mucous membrane of the bladder is involved, a symptom which has been reported in only about one-third of the recorded cases.[3]

Objectively, there are two findings of great importance: 1) A majority of these cases present a palpable mass which is painful on pressure; 2) the cystoscopic picture. This will vary depending on the presence or absence of mucous membrane involvement and, if present, the degree of such involvement. Either a bulging tumor mass covered by normal bladder epithelium will be found or the so-called "typical cystoscopic picture" will be present. Moore et al.,[3] after a careful review of the literature and the reported cases, have constructed a composite picture. While the description is of more interest to the urologist than to the gynecologist, it is so classically done that it is believed that you will enjoy exact quotation. "One would find an elevated area in the bladder 1, 2 or more centimeters in diameter. The mucous membrane surrounding the tumor would be markedly congested and edematous. This edematous mucous membrane would be thrown into folds. Through the usually intact mucous membrane overlying the tumor one could see many cysts, some translucent, other having a bluish cast, while still other cysts would be filled and markedly distended with blue-black material. During menstruation one would find the tumor larger, more congested, with fewer translucent cysts and more bluish cysts. Active menstruation of these tumors might hinder the cystoscopic examination."

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[1] Read at meeting of Miami Obstetrical and Gynecological Society, Miami, Fla., March 10, 1949.

[2] Kretschmer, H. L.: J. Urol., 53: 459–465, 1945. (A lengthy bibliography accompanies this paper. *Editor.*)

[3] Moore, T. D., Herring, A. L. and McCannel, D. A.: J. Urol., 49: 171, 1943. (A bibliography of all reported cases to 1943. *Editor.*)

Biopsy is not always reliable, as will be seen in the case here reported. Transurethral biopsy, as has been aptly stated, might be of greater value in eliminating bladder carcinoma than in diagnosing endometrioma.

TREATMENT

If a patient has no desire for more children or is nearing the menopause, surgical extirpation of the bladder mass is not indicated because surgical removal of the ovaries or sterilization by radiation will cause the tumor to retrogress. If the patient is young or desires more children, conservation of the ovaries is important, and segmental resection of the bladder, if feasible, is indicated for the alleviation of symptoms. These tumor masses are not encapsulated and transurethral fulguration or attempts at resection transurethrally would seem to be contraindicated.

CASE REPORT

Mrs. H. S., aged 34, white, was referred in July 1943 with complaint of "pain in the bladder on urination and whenever the bladder is full." She had undue frequency and no hematuria. The symptoms were slightly exaggerated during the first two days of menstruation. The duration of the symptoms was 18 years. She commenced to menstruate at the age of 15. About a year later her symptoms began and she underwent a diagnostic cystoscopy, which was reported as negative, but was followed by hematuria which lasted 3 weeks. One week after the cystoscopy she had an appendectomy and uterine suspension. In 1943 she had a dilatation of the cervix and removal of the gallbladder, at which time a local surgeon found a "mass on the bladder."

She was then referred for urological study. The urine showed 1 to 3 pus cells per high powered field in centrifuged specimen. Cystoscopy revealed a 3 by 4 cm. broad based tumor situated far behind the trigone in the midline. The surface was smooth, and covered with normal mucosa and no ulceration. Diagnosis: benign bladder tumor. Nine days later transurethral resection of the tumor was done and the patient left the hospital 5 days later. Biopsy report: "Section of the bladder consists of two different features: First, an edematous connective tissue containing numerous myxomatous cells rich in vessels and offering also numerous cells loaded with lipoid and hemosiderotic pigment. Other parts showed the covering epithelium sending pocket into deeper layers which are outlined by a hyperplastic epithelium which in it's part is completely mature and which is surrounded by a moderate chronic inflammatory reaction. There is nowhere evidence of malignancy. Diagnosis: benign edematous myxofibroma, chronic hyperplastic cystic cystitis" (Rezek).

Five days after the patient left the hospital, bleeding developed which necessitated hospitalization, fulguration of the bleeding point and transfusion. Twenty-four days after the initial hemorrhage the patient had to be hospitalized again and bleeding point coagulated. Subsequently a bladder examination revealed the lesion completely healed. Fifteen months after operation, cystoscopy revealed a recurrence of the tumor, smaller than before but immediately adjacent to the previous site. After being reassured by the pathologist, expectant treatment was advised. In early 1948 her symptoms had become worse, and bimanual examination revealed the tumor to be larger and more painful. Segmental resection was done after removing a large cystic left ovary and extraperitonealizing the bladder. The uterus was fibroid in character. The patient went home 13 days later. Pathology report: "Sections taken from the tumor removed from the bladder show an interlacing connective tissue and smooth muscle tissue with island of typical endometrial tissue consisting of endometrial glands and stroma. Diagnosis: endometriosis; adenomyosis" (Rezek). Later the patient had x-ray treatment, 1000 r, both anteriorly and posteriorly, for castration effect. She ceased menstruating 2 months after x-ray treatments. On March 8, 1949 the patient was symptom-free, the urine showed only an occasionaly pus cell and, by cystoscopy, the bladder was entirely normal except for a very slightly elevated area at the old tumor site 1 cm. across which was covered by normal mucous membrane.

COMMENTS

A very pertinent observation has been made in these cases; that is, that patients with endometriosis have almost invariably sustained trauma from previous surgery or have concomitant pelvic disease. This would seem to lend credence to the extension and invasion theory of genesis and substantiate the observation of Goodall:[4] "An effort has been made to classify bladder endometriomata as primary or secondary. This subdivision I cannot endorse because I have tried to demonstrate that all cases of endometriosis of whatever type or whatever pelvic site, are endometrial in origin."

SUMMARY

A case of endometriosis of the bladder is reported.

If a patient's bladder symptoms are unduly exaggerated during menstruation, or if there is proven hematuria during this period, she should have the advantage of cystoscopic study.

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[4] GOODALL, J. R.: Ann. Surg., 120: 891–900, 1944.

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SOME OBSERVATIONS ON THE TECHNIQUE OF TRANSURETHRAL PROSTATIC RESECTION[1]

JOHN B. WEAR

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That intravascular hemolysis can and does occur during endoscopic revision of the enlarged prostate has become an established fact. The amount of plasma hemoglobin will increase as more or large capsular veins are opened and the operation prolonged. If the irrigating fluid is under sufficient pressure to permit vision then obviously it is greater than venous pressure and the fluid may enter the circulation. Visual evidence of this may be obtained by switching to 25 per cent Hippuran under pressure while the veins are open (fig. 1, *A*). From 12 to 15 minutes later a pyelogram is obtained (fig. 1, *B*).

Before the operation the plasma hemoglobin was none and immediately afterwards it was 163 mg. per cent, and 24 hours later again, none. The patient was discharged 8 days postoperative and then x-rays were again taken 8 days later, or 16 days after his operation, under the same conditions in order to check the original finding (fig. 1, *C* and *D*). No pyelogram was obtained.

Another patient was resected down to the capsule and several venous sinuses opened, and again 500 cc Hippuran under pressure was placed in the bladder. This picture (fig. 2, *A*) shows the medium escaping from the capsules and into one large vein, and 15 minutes later (fig. 2, *B*) a pyelogram is obtained.

On other occasions a resection was done without resecting to the capsule, and without opening veins (fig. 2, *C* and *D*) and no pyelogram was obtained.

The mechanism whereby one patient shows severe symptoms from hemolysis and another does not is not well understood. It is not directly proportional to the amount of plasma hemoglobin, as a lower nephron nephrosis may develop at 93 mg. per cent and not at 163 mg. per cent. It is doubtful that the distilled water is entirely at fault as it has repeatedly been injected intravenously without causing symptoms. As much as 1000 cc has been given without appreciable hemolysis. How much hemolysis takes place within the bladder before the fluid enters the vein is difficult to determine but certainly this can be a factor. One does not need much imagination to realize that the prostate itself is the source of much toxic material as the operation proceeds.

For many years it has been recognized that when a hypertrophied prostate is enucleated the compressed portion near the fibrous capsule is not removed. They did not recur very often and the long term results were considered satisfactory. While doing perineal prostatectomy I collected several pieces of the capsule (fig. 3) in order to see what was remaining. From this we can see that as the capsule is approached, the blood vessels become more numerous, and can see why more venous sinuses are opened. Is it possible that we should find it neces-

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[1] Read at annual meeting, North Central Section, American Urological Association Des Moines, Iowa, October 29, 1948.

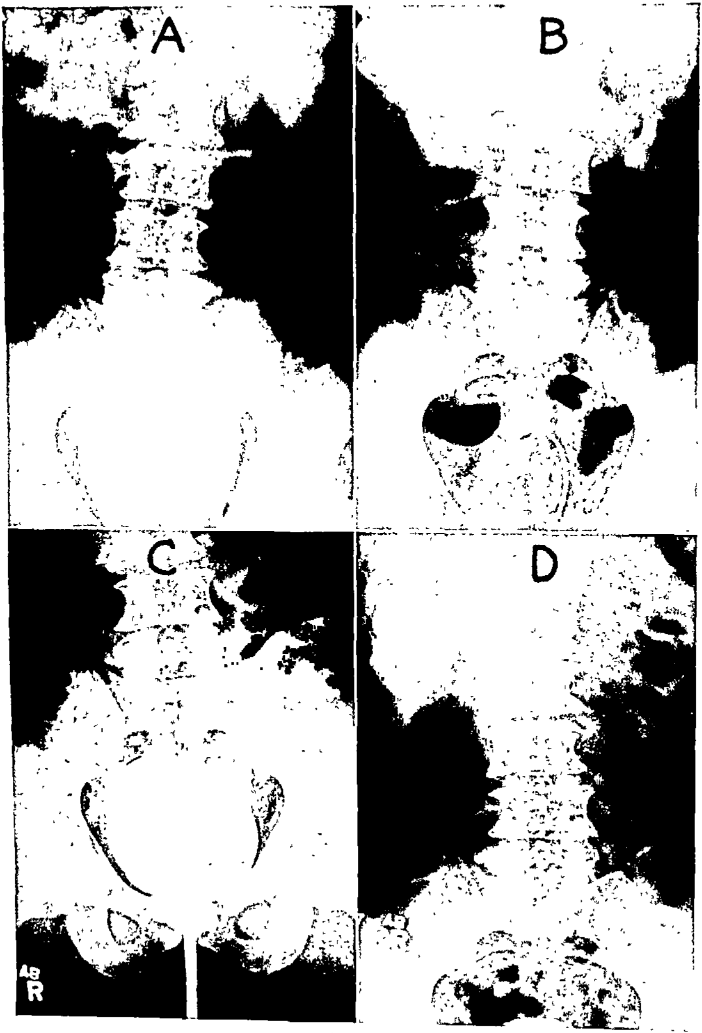

Fig. 1

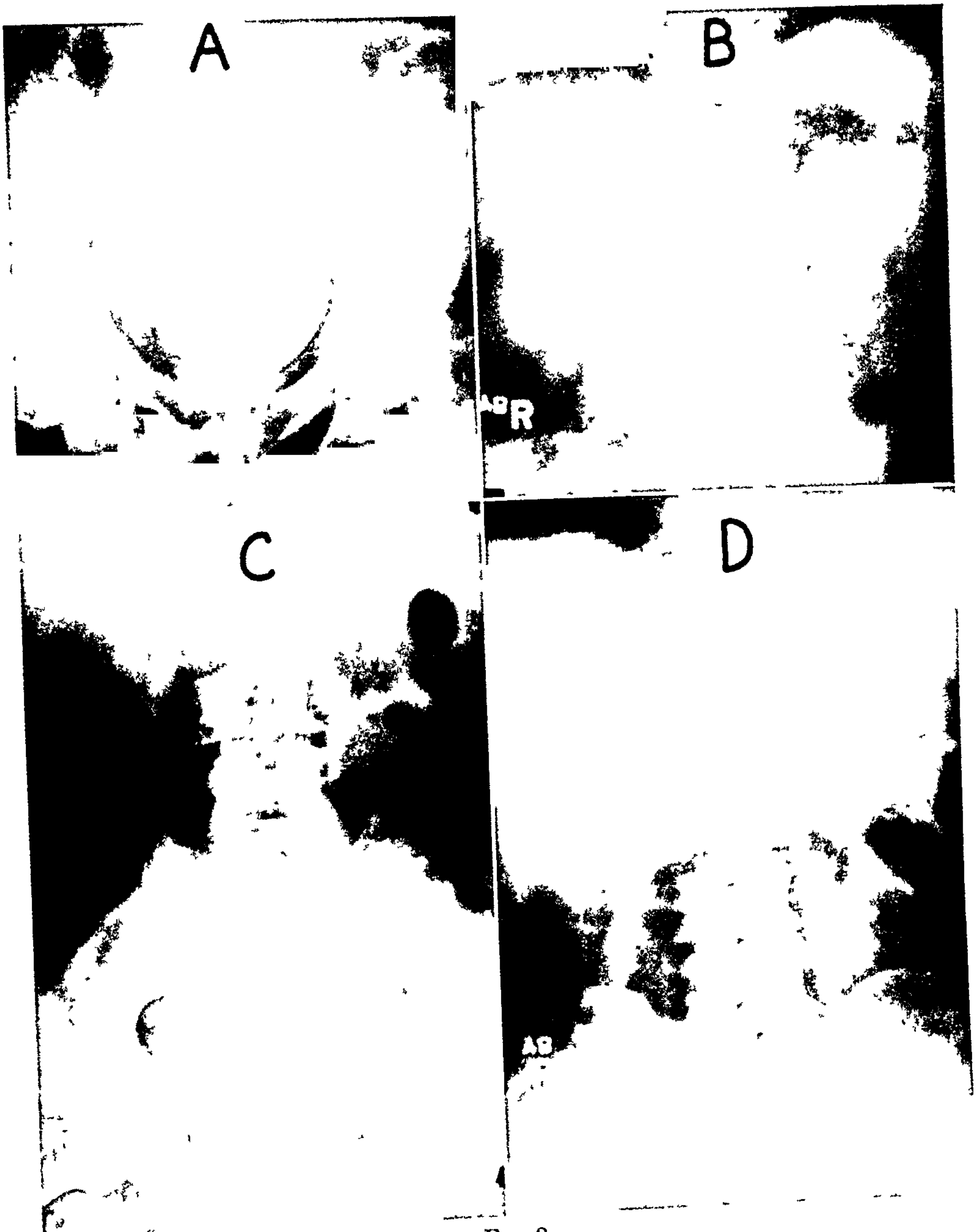

FIG. 2

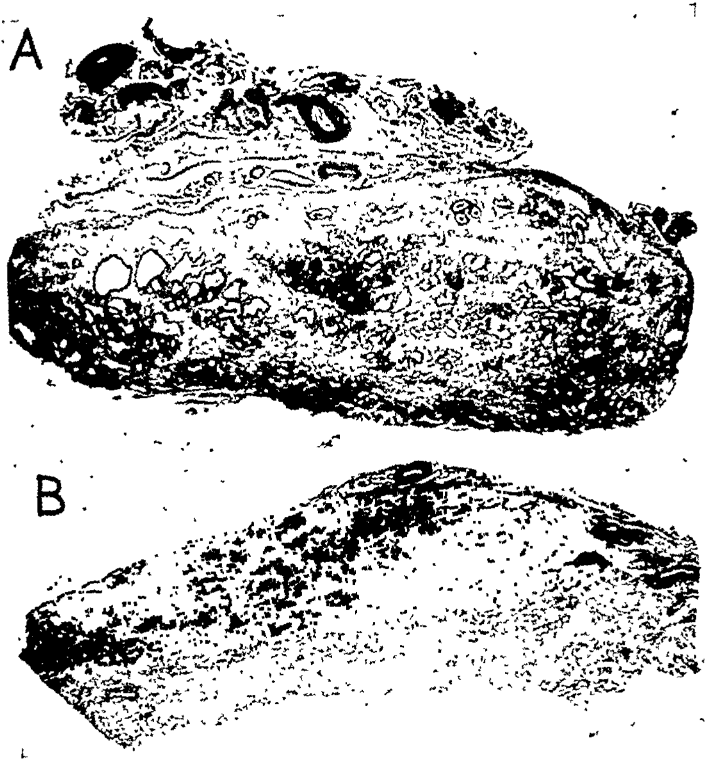

Fig 3

sary or desirable to do more in transurethral resection than is done by an enucleation of the gland?

Transurethral prostatic resection can be safely done with distilled water if the operation is not unduly prolonged, and if venous sinuses near the capsule are avoided. If a large vein is opened the operation should be terminated then and there. Much remains to be learned about intravascular hemolysis and lower nephron nephrosis but shock, toxic substances from the prostate itself, and the action of the fulgurating current on the blood must all be recognized as contributing factors when the irrigating medium enters the blood stream.

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PROSTATIC INFARCTION[1]

RUSSELL B. ROTH

From the Urological Clinic, St. Vincent's Hospital, Erie, Pa.

The principal question to be settled in respect to infarction of the prostate is whether it is a condition of academic interest only, or whether it is of practical significance which demands general recognition. If one is aware that infarcts of the prostate are common, and that the squamous epithelial metaplasia which accompanies them may simulate carcinoma to a degree which may lead to misdiagnosis, then the subject at once becomes important. In our clinic, this situation has arisen, and a review of the scanty literature on the subject clearly demonstrates that it has arisen elsewhere. If it be true that incorrect diagnoses of prostatic carcinoma are being made on histopathological grounds, it must follow that patients are being subjected to orchiectomy or long courses of estrogenic therapy unnecessarily. It may also follow that the occasional case will be evaluated as a prolonged arrest or an actual cure credited to such therapy.

It may be that some standard textbook of pathology or urology makes mention of this condition. We have been unable to find such a reference. Abeshouse, in 1933, gave considerable attention to prostatic infarcts, discussing their possible pathogenesis and mentioning that in 2 of his 3 reported cases, the pathologist's report had erroneously labelled the condition carcinoma. Kasman and Gold, in 1933, reported 2 cases of epithelial metaplasia in the prostate, one of which was associated with an area of infarction. Hubly and Thompson described the clinical aspects of infarction and made mention that in 1 case acini at the periphery were altered in such a manner as to suggest carcinoma. Culp, in 1939, presented a study of 8 cases, including a review of the original 3 cases described by Abeshouse, in which he clearly showed that peripheral metaplasia is a fairly consistent accompaniment of infarction in the prostate, and that 5 of his 8 cases had been originally misdiagnosed as carcinoma. In his monumental study on the morphology of prostatic hyperplasia, Moore completely described the process of infarction and gave the only acceptable figure as to its incidence. Baird and Kimmelstiel, in 1946, presented a study based on 30 cases. Ash and Friedman illustrated the condition in the *Atlas of Genito-Urinary Pathology* issued by the Army Institute of Pathology. In 1947, Rogers presented the clinical and pathological data on 2 additional cases. There has been, then, an authoritative though slender literature on the subject, but it has not won widespread recognition. It is our observation, in discussing the matter with assorted pathologists and urologists over a period of the last 9 years, that few of them are aware of the condition and the problem it occasionally poses.

The hope of the present study is to promote a greater familiarity with these changes. The surgical-pathological material from 220 prostatic operations has been reviewed, with the identification of 18 examples of squamous epithelial

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[1] Read at annual meeting, Northeastern Section, American Urological Association, Seigniory Club, Quebec, October 13, 1948.

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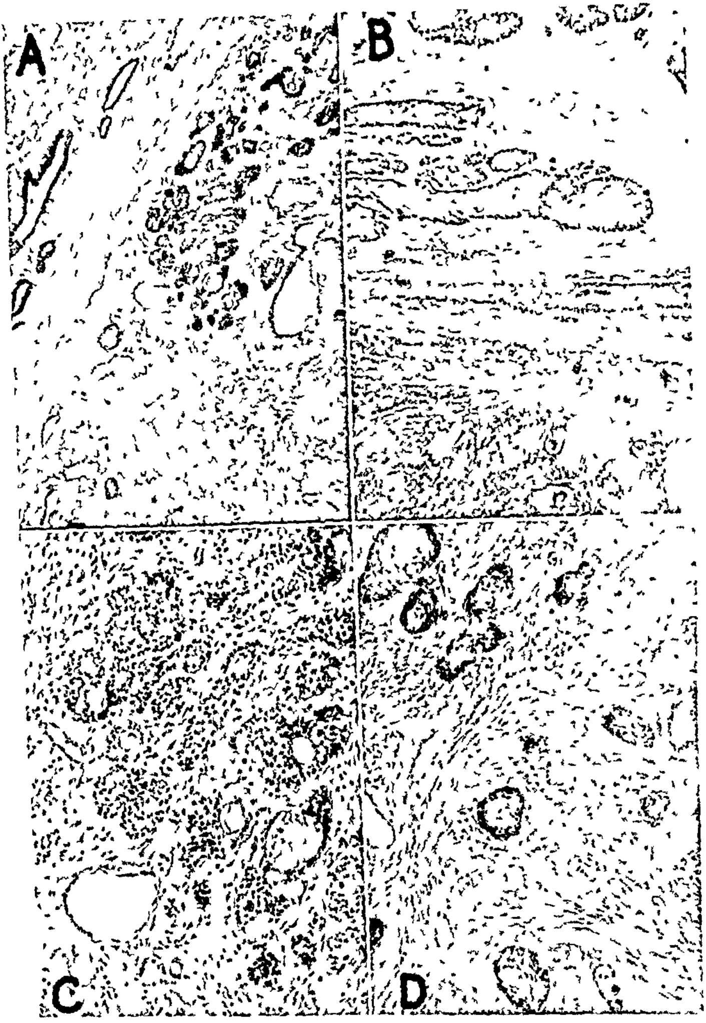

FIG 1 *A*, margin of typical fresh infarct of moderate size *B*, typical compression of acini with elongation and metaplasia into solid cell cords *C*, squamous metaplasia at margin of a fresh infarct Superficial resemblance to carcinomatous architecture is apparent *D*, islands of metaplastic epithelium in an older healed infarct

but voiding resumed after 2 catheterizations Thereafter, he had frequent attacks of retention, but took care of this by self catheterization One and a half years previously, he had been hospitalized for bleeding and acute retention. Operation had been advised but refused. Two weeks before the current admission, he again went into retention, and thereafter was unable to void spontaneously. The day before admission, his catheterized urine was grossly bloody, and finally, he could obtain no urine at all. Cystoscopy was unsatisfactory because of the rapid and uncontrollable bloody ooze from the bladder mucosa overlying the hugely enlarged prostate. A diagnosis of infarction in an hypertrophied prostate was made. Suprapubic cystostomy was done with removal of much blood clot. The generalized bloody ooze from the prostatic projection into the bladder was controlled only by pouring topical thrombin into the bladder. The bladder was closed on a cystostomy tube since the poor condition of the patient contraindicated prostatic enucleation. Nineteen days later, a second-stage suprapubic enucleation was carried out. Convalescence was uneventful and the functional result has been good. Pathological examination of the 180 gm. prostate yielded an initial report of carcinoma of the prostate. Critical review of the sections showed multiple fresh and old areas of infarction. In every instance, the suspected areas of malignancy were found to be confined to the margins of the infarcts, and the impression of carcinoma was discarded.

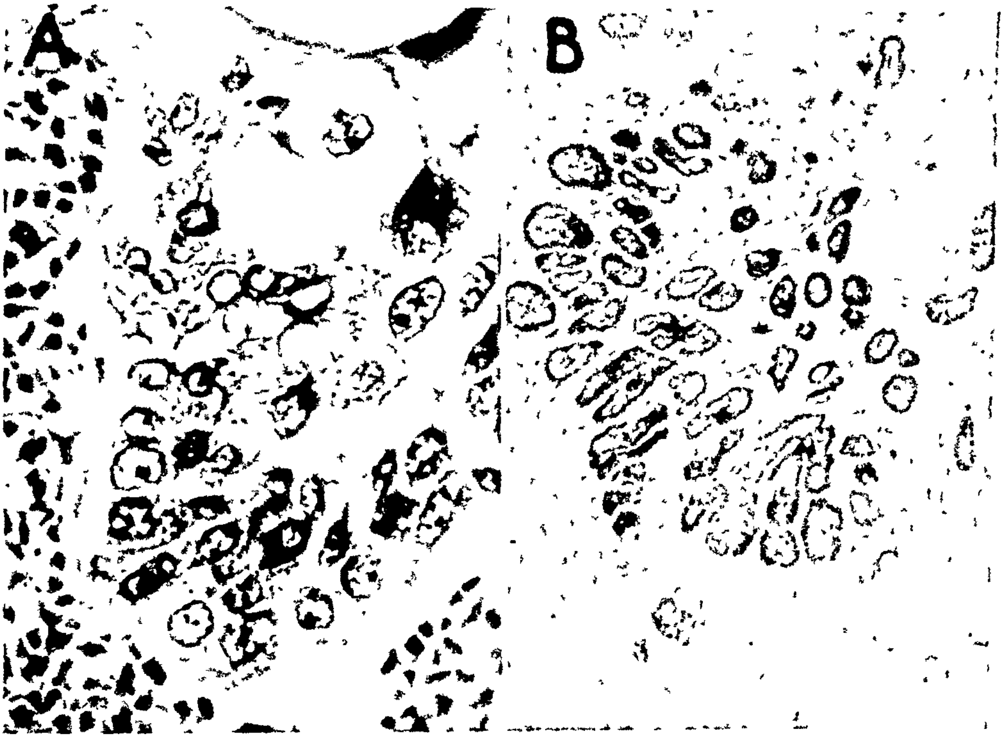

FIG. 2. *A*, high power view of margin of an acinus, showing squamous metaplasia. *B*, low power view of an old healed area of infarction in which only metaplastic acini in fibrous stroma remain.

The features leading to a suspicion of massive infarction, therefore, are the sudden onset of retention wherein the retained urine is found to be grossly bloody or full of clots, and an associated large, tense, non-indurated gland by rectal palpation. The cystoscopic appearance of diffuse oozing of blood from the overlying mucosa, and a bluish alteration in the color of the mucosa may also support this impression

It has been pointed out by Hubly and Thompson that the swelling accompanying infarction may be the factor plunging certain patients into acute retention, and that when a sufficient period of catheter drainage has allowed the infarcted tissue to regress in size, the obstruction no longer is present Rogers has suggested that in cases where the swelling due to infarction is the principal obstructive feature, it might theoretically be possible to maintain the patient on catheter drainage until the infarcted tissue has become shrunken In this way, operation might be avoided We know of no instance in which this has been given practical application In case 2, presented above, 10 days was an insufficient time to allow appreciable decrease in size

Of far greater significance is the matter of avoiding a mistaken diagnosis of malignancy When one receives a definite diagnosis of prostatic carcinoma on a surgical specimen, he must decide whether or not he will subject the patient to a radical perineal or retropubic prostatectomy, or whether he will employ estrogenic hormones or orchiectomy Usually, he will decide to follow one or more of these courses The inference is obvious A mistaken diagnosis leads to unnecessary treatment

We subscribe to the original speculation by Abeshouse that a number of cases must have been called malignant which were in reality benign This may well be a factor responsible for the occasional lengthy survival after "proven" microscopic diagnosis of carcinoma It would be undesirable to credit a prolonged arrest or even a cure of prostatic carcinoma to hormonal therapy or castration now that these methods are being so widely applied

SUMMARY

Infarction of the prostate is a common occurrence in glands displaying nodular hyperplasia

Squamous epithelial metaplasia frequently develops about the periphery of an area of infarction

If one is unacquainted with this process, he may be misled into considering the condition a malignant tumor

Acknowledgement Much valuable cooperation in evaluating the material reviewed in this study has come from Dr Kenneth L Burt, pathologist at St Vincent's Hospital, Erie, Pennsylvania and Drs E L Armstrong and James E Wallace, pathologists at Hamot Hospital, Erie, Pennsylvania

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LYMPHOSARCOMA OF THE PROSTATE

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Lymphosarcoma of the prostate gland is a rare condition. In fact, sarcoma of any type is unusual in the prostate.

The first case of lymphosarcoma of the prostate was reported by Coupland in 1877. It was not until 1902 that Kaufman reported the second case. In 1907 Confort and Favento presented a case in a man 45 years of age. Lefmann also reported a case the same year. Quinby reported another in 1920. In 1923 Symmers reported a case but did not consider any of the other cases reported as acceptable except that of Coupland. Taschiro, in 1924, reported a case which resembled leukemia with splenomegaly, but which at autopsy proved to be a lymphosarcoma of the prostate. In 1925 Bumpus reported 2 cases in men 28 and 64 years old. Zeno, Cid, and Ercole brought forth another case in 1931. Their case was 28 years of age. In 1932 Ferguson and Stewart had a case in a 36 year old patient. Mason in 1933 reported another case. Cole and Martin had a case in 1934 and Dial also had another case the same year. Wegelin in 1935 reported a case in a 68 year old patient. In 1937 Smith reported another case. Rathbun and deVeer reported a case in 1938 but their case had involvement of other regions and was not considered primary in the prostate alone. Counseller and Bedard reported a case in 1940 in a 29 year old patient. Kaufman and Wright had another in 1941. Melicow, Pelton, and Fish reported a case in 1943 and the same year Kirshbaum, Lakin, and Culver also had 1 case.

We recently had a case of lymphosarcoma of the prostate under our care at the Indianapolis General Hospital and desire to add the case to the literature.

CASE REPORT

Indianapolis General Hospital Clinic No. 236107, a Negro, 68 years old, was admitted February 6, 1948 with the complaints of weakness, moderate loss of appetite and a feeling of uncertainty in all body movements. Illness had begun insidiously 6 to 8 months prior to admission but he had not gone to a doctor until he had several severe prolonged nose bleeds in January 1948. He complained that in walking he could not control the movements of his feet and legs and had to hold to something for support. His wife had noted some mental confusion and emotional instability. He had been mildly constipated for 1 month. There was some difficulty in starting the urine but there had been no blood in the urine and no pain with its passage. He had suffered no serious illnesses in his past life.

Physical examination: Temperature 97.2 F, respirations 20, pulse 90, blood pressure 148/88. The patient responded slowly to questioning but seemed not to be confused. Nutrition was fair. There was a soft, blowing, systolic murmur audible at the apex of the heart. The chest was normal and there were no abnormal findings in the abdomen. Reflexes were normal and there was good co-ordination, but marked muscular weakness was present in the legs, particularly in the hamstring group of muscles.

Laboratory examination on February 6, 1948: Erythrocytes 2.89 million, *hemoglobin* 8.3 gm., leukocytes 8950, with 64 neutrophiles, 2 band forms, 1 eosinophile, 28 lymphocytes and 5 monocytes; there were macrocytes, target cells and cells showing hypochromia and polychromatophilia. Urine was acid in reaction, had specific gravity of 1.022, no albumin or sugar and contained 1 or 2 pus cells per high power field. Klein and Kahn tests were negative. Chest film showed increased bronchial markings and perivascular fibrosis.

During the following few days the physical condition remained unchanged, while the mental state was unstable, being marked by periods of irrationality, delusional ideas, hallucinations and restlessness. Whole blood transfusions of 500 cc. were given on February 10 and 11.

Further laboratory studies were as follows: February 7, nonprotein nitrogen of blood 30 mg. per 100 cc.; February 11, serum acid phosphatase 2.4 units. The cerebrospinal fluid was tapped on February 11 and was found to be grossly normal with normal dynamics. The spinal fluid total proteins were 56 mg. per 100 cc., the sugar 94 mg. per 100 cc., the Pandy 1 plus and the Wassermann was negative. Colloidal gold reaction was 0112110000.

On February 19, his only complaints were those of nose bleed and sore throat. A rather profuse post nasal discharge was noticed. Laboratory work on this date was as follows: Blood platelet count 200000 per c. mm., fragility of erythrocytes normal, prothrombin time 20.7 seconds (control 15.0 seconds), coagulation time 2 minutes 24 seconds, bleeding time 3 minutes 28 seconds, mean corpuscular volume 90.3 cubic microns, mean corpuscular hemoglobin 28.7 micromicrograms.

On February 21, there was moderate bilateral enlargment of the submaxillary lymph nodes and a firm nodule was found in the thyroid gland. A peculiar fungating nodule in the skin of the left forehead was noticed on February 22 and was removed for biopsy study. A pathologic report on March 4 stated that the structure of the nodule was that of "a granuloma, compatible with histoplasmosis." Dr. Paul Fouts examined the patient as a consultant on March 4 and did a biopsy of sternal bone marrow. His report stated that there was myeloid series hyperplasia, but no immaturity; in the neutrophils from the buffy coat of the citrated marrow were numerous round, blue-staining, capsulated objects having the size, shape and staining characteristics of Histoplasma capsulatum.

X-ray examination of the colon had been done on March 1, 1948 and reported as negative. Roentgenographic studies of the stomach, esophagus and duodenum were normal on March 22 and the colon was again considered to be normal. The blood was cultured for histoplasmids and reported negative on March 5 and April 2 and the bone marrow culture for these organisms was reported negative on March 22. Sternal marrow examination on the last date was negative.

On March 15 the coagulation time had been 2 minutes 32 seconds (Lee and White method) and the bleeding time 7 minutes 26 seconds. Clot retraction was complete in 2 hours and prothrombin time was 17 seconds (control 16 seconds). On March 30, hemoglobin was 13 gm., and leukocytes numbered 9400, including neutrophiles 69 per cent, bands 3 per cent, metamyelocytes 1 per cent, lymphocytes 26 per cent and monocytes 1 per cent.

The clinical course of this patient up to the third week of April had been that of a prolonged, cachectic illness with gradual failure of nutrition and occasional elevations of temperature. Nothing in the physical or laboratory examinations provided any clue to the fundamental nature of the illness until a suprapubic mass was found on May 13. This was considered to be a distended urinary bladder until catheterization withdrew only 150 cc of urine and left a firm suprapubic mass. Also noted for the first time was a firm nodule 2 cm. in diameter slightly above and medial to the left anterior superior iliac spine within the abdominal cavity. Repeated enemas failed to produce any change in the position or size of these masses.

One of us (J.W.) examined the patient on May 15 and noted a distended urinary bladder with its upper level almost at the umbilicus, residual urine now of 540 cc, a long urethra due to enlargment of the prostate gland, which was boggy, tender and filled the rectal canal. A catheter was anchored and drained well until May 22 when gross blood appeared in the urine and clots filled the bladder. The bladder was irrigated with difficulty, and a cystogram (fig. 1) on May 24 showed elevation of the bladder with very great displacement to the right at the bladder neck by a mass at the left of and below the bladder. The impression was that there was a neoplasm confined to or adjacent to the left lobe of the prostate. The films of the colon were reviewed and the sigmoid found to be displaced upward and to the right. (Fig. 2, *A* shows a thin stream of barium in the sigmoid in the right oblique position; fig. 2, *B* shows barium-filled sigmoid in anteroposterior position.)

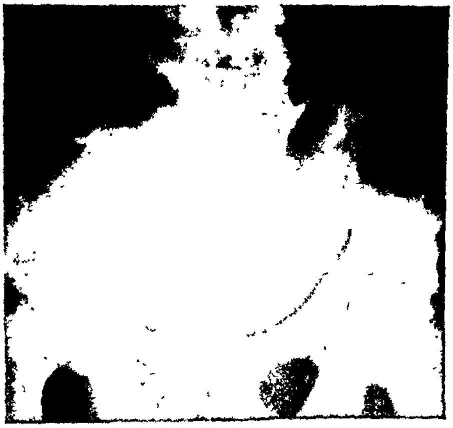

FIG. 1

The condition of the patient was progressively and rapidly deteriorating now though he responded to requests. Nutrition was sustained largely by intravenous infusions. A note was made by one of us (W.A.S.) in the course of a ward round that it was still difficult to become properly oriented with regard to this patient's illness and that a smooth, firm, nonnodular mass, possibly connected with and certainly immediately adjacent to the left lobe of the prostate gland could be palpated per rectum and the impression was that this was probably a retroperitoneal sarcoma.

By June 2, the patient was very weak, the catheter could be removed, cleaned and reinserted with difficulty and pain and bleeding occurred with this operation. A No. 20 Robinson catheter was anchored but it was impossible to keep it patent due to blood clot formation. A septic fever began on June 5, the retroperitoneal mass was felt to have become larger by June 13 and death supervened 3 days later.

At no time had there been marked deviation from normal in the leukocytic elements of the blood.

Autopsy (Dr. William Dublin): The bladder, prostate, and rectum were removed together. Between the bladder and the rectum, there was a mass, roughly rounded, 13.0 cm. in diameter, which filled the true pelvis, and on palpation and inspection, originally in the cul-de-sac, it presented as a rounded eminence posterior and to the left of the bladder. The urethra assumed an S-shaped channel as a result of bulging into it of the mass. From the back of the lower bend of the "S", which pointed posteriorly, there was a blind pouch 3.0 cm. in diameter. This was hemorrhagic; from it extended a further channel 0.4 cm. in diameter over a distance of 2.0 cm., which could represent the path of catheter or instrument. All the vesical and urethral mucosa was hemorrhagic, but otherwise was intrinsically unaltered except by extrinsic encroachment by the mass. The rectal mucosa appeared uninvolved. The prostate and seminal vesicles could not be found; they had been destroyed completely by the mass. Tissue of the mass was pink to gray in color, with delicate fibrous strands and with a succulent, meaty texture in general. This would suggest neoplasm, possibly sarcoma.

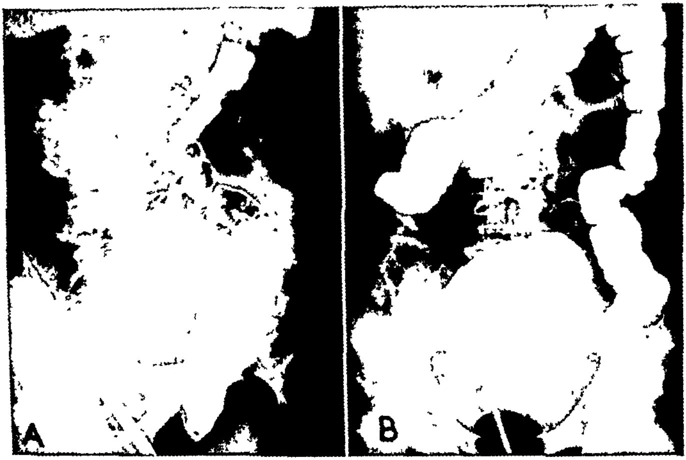

FIG. 2

Microscopic examination revealed infiltration of the prostate gland by closely packed masses of lymphocytes. There was slightly more than the usual degree of deposit of connective tissue fibers and, in certain places, the adventitia of blood vessels contained tumor cells. The tumor would seem to be a lymphosarcoma with a very slight tendency to differentiation toward a connective tissue type.

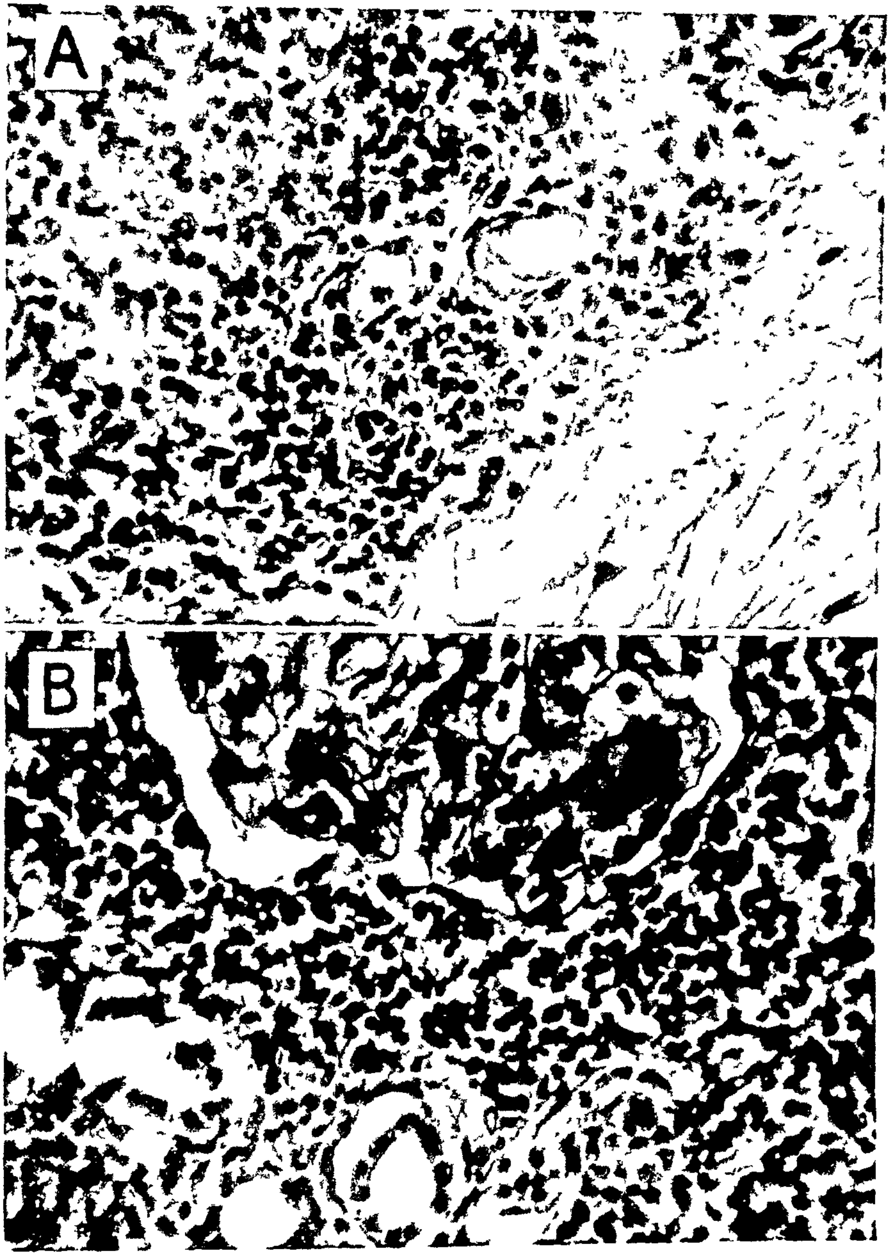

Fig 3

Similar infiltration was found in the lungs, liver, stomach, kidneys, urinary bladder wall and abdominal lymph nodes. The prostate gland was the site of most massive tumor formation. Fig. 3, *A* shows the infiltration of the prostate by lymphocytes and some connective tissue elements; fig. 3, *B* represents a section of a kidney showing a similar pathology, a portion of a glomerulus appears in the upper area of the field

DISCUSSION

There has been some question in the past as to whether or not such a condition can occur in the prostate The very fact that each few years a case is reported which has been reviewed by an able pathologist should tend to settle this question

Foot states that true lymphosarcoma of the prostate is very rare, since the organ has little association with lymph follicles He further states that when lymphosarcoma does occur in the prostate, it differs little from those found in other situations

Ewing questioned the occurrence of primary lymphosarcoma of the prostate on the grounds that the prostate does not contain adenoid tissue and says that the so called lymphosarcoma in reality is nothing more than extremely anaplastic small cell carcinoma However, Kaufman and Wright state that in a recent personal interview with one of them, Ewing admitted the possibility of a lymphatic tumor in the prostate gland

Symmers says that the prostate belongs to the auxiliary lymphatic system in that it contains interstitial lymphoid foci which, though often overlooked, are readily seen in certain conditions The infrequency of this type of tumor, he points out, is due to the fact that the lymphoid cell rests are numerically insignificant, functionally dormant, and undergo hyperplasia only under unusual circumstances

Wegelin believes that in the prostate, lymph follicles, although normally absent, may evolve as a part of an inflammatory reaction

Fukase was able to demonstrate lymphoid tissue in a series of 222 prostates and says that he is of the opinion that this tissue may become hyperplastic following inflammatory conditions in the lower genito urinary tract He says that small, primitive, or rudimentary lymph nodes occur normally throughout the prostate in the form of very small aggregations of lymphocytes located beneath the glandular and duct epithelium, most marked toward the outlets of the ducts

While sarcoma of the prostate has been considered a disease of youth, the average age of the lymphosarcomas reported is 41 years The youngest was 22 years and the oldest was 68 years of age Bumpus has said that a tumor of the prostate in a young person is most often sarcoma So far as we know there have been no cases of lymphosarcoma reported in children The age of our patient was 68 years

The symptoms of lymphosarcoma of the prostate are usually those of vesical neck obstruction In our case the patient had complete retention He also had severe gross hematuria It was believed that he was too poor a risk when first seen to undergo cystoscopy When a urethral catheter was anchored, we found that he had a very long urethra Rectal examination revealed a prostate which was large but not hard or nodular It felt somewhat like a prostatic abscess This unusual feeling to the examining finger is characteristic of lymphosarcoma of the

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ELEVATION OF SERUM ACID PHOSPHATASE FOLLOWING PROSTATIC MASSAGE

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Normal serum acid phosphatase levels vary from 0.0 to 0.7, recorded in Bodansky units. High values indicate metastatic prostatic carcinoma. Fluctuations in the levels of individual patients under altered circumstances are not listed in the literature. That such variations may occur and even reach high enough levels to permit an inaccurate diagnosis of metastatic carcinoma of the prostate gland is illustrated by the following case:

Mr. S. H., a 73 year old white man, was admitted to the urological service of Charles S. Wilson Memorial Hospital on October 16, 1948 with complete urinary retention. Blood samples were taken for routine blood count, nonprotein nitrogen acid and alkaline serum phosphatase; prostatic secretion for a Papanicolaou stain was obtained. A 16 Foley catheter was anchored in the bladder and 950 cc residual urine evacuated. Laboratory data were as follows: Urine: 3+ albumin, red and white blood cells, specific gravity 1.006; blood nonprotein nitrogen, 63 mg. per cent; red blood cells 3,890,000, hemoglobin 10.5 gm.; white blood cells 8,200 with normal differential; prostatic secretions negative for tumor cells; acid serum phosphatase 1.6 Bodansky units; alkaline serum phosphatase 2.6 Bodansky units. The high acid phosphatase level appeared to be convincing evidence of metastatic prostatic carcinoma. On rectal examination, however, the prostate was found to be 3+ enlarged, regular, smooth, and of normal, elastic consistency, in no way suggestive of carcinoma. Acid and alkaline serum phosphatase were repeated 2 days later. The reports were: acid serum phosphatase 0.9, alkaline phosphatase 3.0. Five days later or 1 week after the initial tests the acid phosphatase was 0.2 and the alkaline phosphatase 3.5 Bodansky units.

In view of these discrepancies in the acid serum phosphatase levels, the matter was discussed with the resident in urology and the laboratory personnel. Sources of error in carrying out the laboratory procedures were ruled out. The resident recalled that the prostatic massage to obtain secretion for the Papanicolaou stain preceded the drawing of blood for the phosphatase tests.

Our tentative explanation was that prostatic secretion may have been massaged into the blood stream and thus produced a temporary elevation of the acid serum phosphatase. The relatively high phosphatase level 2 days later was presumably due to the patient's impaired renal function, and consequently slow excretion of the phosphatase.

We were unable to obtain a biopsy from the prostate gland because the patient also suffered from advanced pulmonary fibrosis with cardiac decompensation. He was eventually discharged with an indwelling catheter.

This case prompted a study to examine the effect of prostatic massage on serum

TABLE I

CASE NO	PATIENT	AGE	CLINICAL DIAGNOSIS	CHARACTER OF PROSTATE GLAND	BEFORE MASSAGE	AFTER MASSAGE								
						21 min	30 min	40 min	1 hr	2 hr	3 hr	5 hr	24 hr	48 hr
1	R M	55	Chronic prostatitis	1+ Firm to boggy	0.5				2.1	1.1	0.9	0.7	0.1	
2	J B	17	Chronic prostatitis	moderately enlarged Soft to indurated	0.3				0.8	0.2	0.4	0.1	0.1	
3	L S	48	Chronic prostatitis	moderately enlarged Nodular and firm	0.6				0.6	0.5	0.1	0.3	0.1	
4	G K	55	Hypertrophy of prostate	3+ Normal consistency	0.8				0.9	0.5	0.1	0.3	0.3	
5	F L	36	Chronic prostatitis	not enlarged Boggy	0.2				0.6	0.5	0.5	0.4	0.1	
6	L K	60	Cancer of prostate	2+ Very hard, one nodule	0.4	0.6		0.4	0.1				0.1	
7	A M	50	Hypertrophy of prostate	1+ Firm, one hard nodule	0.5	0.6		0.1	0.1				0.3	
8	M M	49	Hypertrophy of prostate	1+ Boggy	0.3	0.4		0.2	0.6				0.3	0.0
9	M I	58	Hypertrophy of prostate	2-3+ Normal consistency	0.2	1.9		4.1	2.9				0.1	0.3
10	F C	63	Hypertrophy of prostate	2+ Boggy	0.2	2.1		1.1	1.2				0.3	0.2

11	C. D.	39	Chronic prostatitis	small Normal consistency	0.0	0.1		0.2	0.2				0.3	0.3
12	M. B.	63	Hypertrophy of prostate, papilloma of bladder	2+ Boggy	0.2		0.8						0.2	0.2
13	S. M.	20	Enuresis	Normal	0.2		0.3						0.2	0.2
14	E. H.	70	Hypertrophy of prostate	1–2+ Soft	0.3		0.5						0.2	0.2
15	M. R.	54	Chronic prostatitis	not enlarged Firm, nodular	0.3		0.3						0.2	0.1
16	J. A.	21	Chronic prostatitis	2+ Soft	0.7		0.2						0.2	0.2
17	J. S.	56	Condyloma acum, of prepuce	1+ Boggy	0.1		0.5						0.2	0.2
18	C. L.	60	Hypertrophy of prostate	2+ Normal	0.1		0.9						0.3	0.3
19	B. L.	56	Hypertrophy of prostate	3+ Boggy	0.0		15.5						0.1	0.2
20	L. J.	26	Cancer of prostate	1–2+ Nodular, stony hard left lobe	0.2		0.7						0.1	0.3

acid phosphatase levels. Acid serum phosphatase determinations were made on 20 out-patients immediately before and at definite intervals after prostatic massage. Within 1 hour after prostatic massage the acid serum phosphatase was elevated above the original level in 17 patients, unchanged in 2 patients, and lower in 1 patient. In 8 patients the acid serum phosphatase had risen to a level above 0.7 Bodansky units, the highest level still regarded as normal. In four of these patients the acid phosphatase reached definite "carcinoma" levels, above 1.0 Bodansky units. In 1 case, the relatively high figure of 0.7 Bodansky units was obtained as late as 5 hours after prostatic massage. After a 24 hour interval, the acid serum phosphatase was lower than before massage in 12 cases, not significantly changed in 6, and somewhat higher in 2 cases. After 48 hours the acid phosphatase levels were similar to the 24 hour figures. An attempt was made to correlate the character of the prostate gland with the elevation of the acid serum phosphatase after massage. In general, massage of larger prostate glands containing larger amounts of secretion seemed to produce greater acid phosphatase elevations than massage of smaller and firmer glands. Details are given in table 1.

SUMMARY

Prostatic massage may produce an elevation of the acid serum phosphatase to "carcinoma" levels. In individuals with normally functioning kidneys, the acid phosphatase level is highest within 1 hour after the massage and may still be relatively high 5 hours after the massage. If the kidney function is impaired, elevation of the acid phosphatase level may be prolonged. Following prostatic massage, acid phosphatase returns to the original level or falls slightly below at the end of 24 hours.

CONCLUSIONS

Acid serum phosphatase determinations should not be performed soon after a prostatic massage. Reliable and accurate values will be obtained 24 hours after massage, if the patient's kidney function is not impaired.

We express our appreciation to Alexander A. Kosinski, M.D. and Miss E. A. Burge, M.T. *of the Department of Laboratories of the* Charles S. Wilson Memorial Hospital.

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Binghamton, N. Y.

11	C. D.	39	Chronic prostatitis	small Normal consistency	0.0	0.1		0.2	0.2				0.3	0.3
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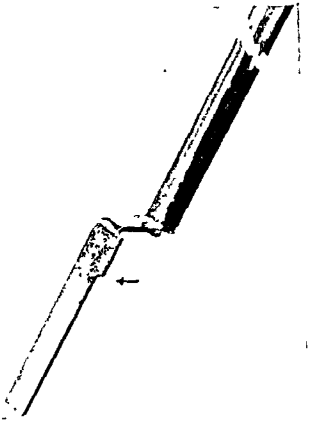

FIG. 2. One of leg supports, showing two steps for adaption to slides of most surgical tables.

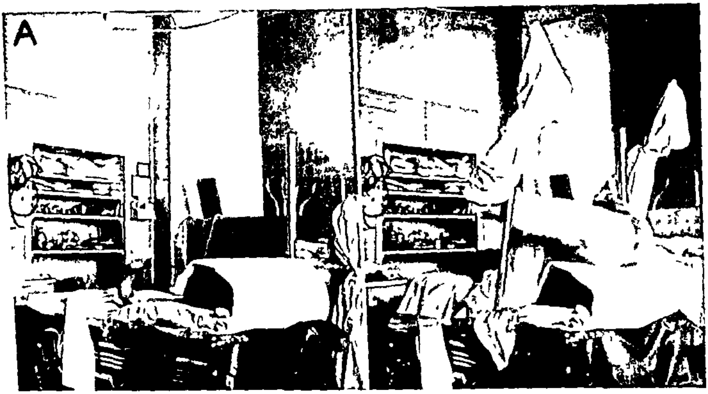

FIG. 3. *A*, table and sponge rubber cushion with one standard up for reception of patient. *B*, patient in perineal prostatectomy position. Note that leg supports have been slid toward patient's head to support thighs in proper position. Patient's body has not been moved.

sponge rubber cushion. The leg supports are made with two steps on them so that they will fit most operating room tables, but not all. Should the hospital where the surgeon works have additional tables, another step could be easily added. The method of using the table is as follows:

Drop the lower segment of the table. Have the table as low as it will go with the shoulder pieces in approximate position and the cushion on the table with one leg support in position. The patient is lifted onto the table, the lower part of the back and buttocks on the rubber cushion and one leg hooked over one of the leg supports. The other leg support is then stuck into the slide. The operator now flexes one thigh to the point where the perineum is in the perineal prostatectomy position, and the leg support is slid back to hold the thigh in this position. The other thigh is then flexed and the leg support is pushed back to an equal position. It is not necessary to lock the leg supports, as the eccentric position of the thighs will hold them fixed. The sponge rubber cushion requires no adjusting. The accompanying illustrations (figs. 1, 2, 3) demonstrate the table and its use.

The advantages of these attachments are these: It is not necessary to have an extra table to put on top of a surgical table. Any operating room table is adaptable. The sliding leg supports permit of any position of the perineum that the operator is accustomed to or may desire. The perineal prostatectomy table is put into position with the greatest of ease in the shortest possible time and with the least trouble to the nursing staff. These leg supports and sponge rubber cushion should be standard equipment for all modern surgical tables, and it is to be hoped that the equipment which I have described will become standard with the manufacturers of surgical tables and be supplied with them.

These accessories may be procured from the R. L. Scherer Co., 2206 West Seventh Street, Los Angeles 14, Calif. Please address Mr. Theodore E. Skeva.

1136 W. Sixth St., Los Angeles 14, Calif.

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URETHRAL DIVERTICULUM IN THE FEMALE[1]

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Until about ten years ago, there were very few references in the literature to diverticulum of the female urethra. Since that time, what has appeared has been found almost entirely in the urologic literature. The symptoms associated with this disease entity are frequently related to gynecologic problems and many times patients with urethral diverticula are seen first of all by gynecologists rather than by urologists. However, the gynecologic literature refers to the situation only rarely.

A few words concerning the anatomy of the female urethra would seem in order before discussion of this interesting pathologic condition. The female urethra has purely a urinary function. It is approximately 1½ inches (about 4 cm.) in length and is analogous to the membranous portion of the male urethra. Its wall contains a muscular, a submucous and a mucous coat. The mucosa is of the stratified squamous type throughout except near the bladder, where it more nearly resembles the transitional epithelium of the bladder. Johnson, Renner and Folsom have called attention to many small tubular glands in the proximal two thirds of the female urethra. However, more detailed and careful histologic study by MacKenzie and Beck, and by Cabot and Shoemaker has definitely shown that such structures do not exist. In the distal one third of the female urethra, just within the external meatus, lie the paired openings of Skene's glands.

The submucosa is a layer of loose areolar tissue. The muscular coat, which is continuous with that of the bladder, is nonstriated, with an inner longitudinal and an outer circular layer. It is not within the province of this paper to discuss the sphincteric action of the urethra and vesical neck in the female. However, undoubtedly it is a combined action bringing into play the muscular fibers surrounding the vesical neck, and those surrounding the urethral canal itself.

Diverticula of the female urethra may be classified as true or false, and as congenital or acquired. The true diverticulum presents all layers of the urethral wall; the false diverticulum shows a break in the continuity of the muscularis and its coat contains only the submusoca and mucosa. The question whether diverticula are congenital or acquired is disputed repeatedly in the literature, and I do not feel that it has been satisfactorily answered. Trauma to the urethra at childbirth and infections of the urethra have been offered as the reason for the belief that diverticula are acquired, but if such be the case, with the frequency of both suggested etiologic factors, we certainly should see this condition more often.

We should like to discuss, after these preliminary remarks, our series of 71 cases up to January 1, 1948. All decades from the third to the sixth were repre-

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[1] Read at annual meeting, North Central Section, American Urological Association, Des Moines, Iowa, October 29, 1948.

sented, the average age being 41 years. Most of these women had had sympt
of urethral distress of long duration, usually 5 to 10 years. They all repo
having had many and varied treatments ranging from local instillations, thr
cautery, to pelvic surgical procedures of one kind or another without ben
It was surprising to note how many of these patients had had their uret
symptoms ascribed to gynecologic conditions of one kind or another. Only
often has an inexperienced surgeon attempted to ascribe the symptoms
woman suffering with a true urinary disorder to pelvic relaxation, pres
of the uterus on the bladder or the like.

The symptoms in almost all instances were referable to the urinary tr
Frequency and dysuria were usually present and their severity varied f
relatively mild distress to tenesmus and even strangury. Hematuria was
common.

Pain was noted in 38 cases, being described as low abdominal, perineal
vaginal. Included in this group were those patients who described their dist
as a sense of weight or pressure in the pelvis.

A vaginal mass was noted in 29 cases, either by the patient or found at
time of examination. Thirty patients complained of the sensation of leakag
urine. In many of these it was only a watery discharge while in others it amoun
to a true stress incontinence. Dyspareunia was mentioned occasionally.

We have observed repeatedly that patients suffering with a urethral diverti
lum seem to present more severe symptoms than patients with granular or ci
tricial urethritis or cystitis. The severity of their symptoms is definitely great
and appreciation of this fact should call to the physician's mind the possibil
of the existence of this lesion. The frequency with which the diagnosis is mis
is largely due, we are sure, to the fact that the lesion is not considered at
time of examination, and is not looked for.

The diagnosis of urethral diverticulum is not always easy to make. The orif
of the diverticulum is usually in the midurethra and may be only the size o
pin point. Occasionally the spontaneous exudation of purulent material m
occur, and if it does, it will call the cystoscopist's attention to the orifice of
diverticulum. This may not occur and unless the lesion is suspected and
floor of the urethra is palpated vaginally against the urethroscope, no secreti
may be seen and the orifice may go unnoticed. In 2 of our patients the orifi
was not in the floor but in the roof of the urethra. Occasionally, vaginal examin
tion may reveal a doughy, rounded mass in the anterior vaginal wall benea
the urethra and pressure on it will cause a discharge from the urethral meat
In our series the diagnosis was made or confirmed by cystoscopy in all cases, a
in approximately 10 per cent of the cases repeated cystoscopy was necessa

The urinalysis does not yield any pathognomonic findings, but we were al
to make a rather interesting observation concerning the variation in the deg
of pyuria in the individual case. If the voided urine was examined, the pyuria w
marked. However, when the catheterized urine was checked, little or no pyu
was present. This fact cannot be considered diagnostic but it does suggest t

at the time of voiding, the urethral musculature squeezes the diverticulum and causes the discharge of its purulent contents

The treatment of diverticulum of the female urethra is primarily surgical Massage of the urethra, dilatation and instillations are frequently of only temporary benefit Cautery done transurethrally has been suggested but we do not believe that it is the procedure of choice Transurethral incision of the orifice of the sac has been beneficial in a few cases Surgical excision through a vaginal approach, the entire sac of the diverticulum being adequately dissected out and removed, has proved most successful Of aid to the surgeon in finding these lesions at operation has been the insertion of a No 4 ureteral catheter transurethrally through the orifice and allowing the same to coil in the sac

In conclusion, some general considerations concerning the symptomatology, diagnosis and treatment of diverticulum of the female urethra have been presented Seventy one cases were included in this series

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DIVERTICULA OF THE FEMALE URETHRA: REPORT OF FOUR CASES, ONE CONTAINING A CALCULUS

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The incidence of diverticula of the female urethra is not too definite. Downer d Virgilio state that the frequency of diverticula of the urethra is unknown. most reports only a few cases have been cited, and even in larger clinics not many cases have been seen. C. M. Johnson quotes Walters as reporting cases in a 10 year period at the Mayo Clinic. Schmitz noted 8 cases in a 10 r period. Menville and Mitchell noted 13 cases in 510,585 hospital admissions. the authors' experience, 6 cases have been observed over a 13 year period. o of which are not recorded here were seen by one of us (E. W. K.) in a year period at another institution. Even though a number of cases have been orted, it still cannot be considered a common lesion.

The etiology of diverticulum of the urethra is considered to be congenital in gin by some writers, namely, Johnson, Parmenter, and McMahon. Johnson ed the possible etiological factors as:

A. Congenital: 1) Gartner's duct; 2) cyst from faulty union of primal folds; cell rest; 4) wolffian duct; 5) vaginal cyst.

B. Acquired: 1) Trauma during childbirth; 2) infection of the urethral glands h sealing off and abscess formation with the opening of the abscess into the thra; 3) instrumentation of the urethra with deep fulguration of urethral ons; 4) stricture of the urethra; and 5) urethral stone.

Perhaps all of these possible causes could be the etiological factors, but this urely academic. Lowsley and Kirwin state that it is impossible to differentiate ween acquired and congenital diverticula. Most writers believe that they are uired, and that they follow infection in the urethral glands, with abscess mation and re-communication with the urethra. (Furniss, Higgins and Ramsek, Engel and others.) It is the authors' opinion also that diverticula must rt with infection, then abscess formation, and later diverticula. It is possible t trauma at childbirth is an etiological factor, but this seems far fetched when considers the number of pregnancies in relation to the few diverticula that seen. In case 2 reported here, instrumentation may possibly have been an logical factor.

Diverticula of the urethra may be classified as either true or false. If true, wall of the diverticula contains all of the coats of the urethra. According to rman and Greene, this is not proven and the term should be discarded, false erticula being the best terminology. In most pathological specimens the walls made up of fibrous tissue with little or no muscle, and with a cuboidal or udo stratified type of epithelium, or none at all. Occasionally a few glandular nents may be present. The opening of the diverticulum in the urethra may large or small, and is usually situated in the middle third of the urethra on floor. There may be multiple openings to a diverticulum (Parmenter), and the sac itself may be multilocular, as was noted in four of Engel's cases. This seems to be added proof to the infectious origin of the lesion. There may be considerable variation as to the size of diverticula, some extending posteriorily along the urethra to lie partially under the vesical orifice.

Calculus formation in a diverticulum is a rare finding. Herman and Greene cite the incidence as 17 per cent. Gaston and Ferrucci in 1939 reviewed the literature collected, 33 cases, and added one of their own, making a total of 34. In 1942 Carter reported the thirty-fifth case. *Higgins and Roen brought the* total to 39. In 1943 Lane's report brought the total to 40. McMahon reported the forty-first case in 1946. Menville and Mitchell cited two in their series, bringing the total to 43. The case reported here should bring the total to 44 cases of diverticula with calculi. Calculi in the diverticula may be either single or multiple. Lane's case was one of multiple stone. The stones may vary also in size. The etiology of stone formation in the diverticulum of the urethra no doubt is dependent upon urinary stasis plus infection. It is believed by some that a stone may migrate from the upper urinary tract to lodge in a diverticulum of the urethra, and there increase in size. This may be quite true, but it seems to be more logical that a calculus in a diverticulum forms in the diverticulum itself. According to Herman and Greene, the composition of these stones are chiefly ammonium phosphate.

The symptomotology is variable, ranging from no symptoms at times to quite severe symptoms at others. Pain in the region of the urethra, soreness, and painful intercourse are quite common. Attacks of urgency, frequency, dysuria, and terminal tenesmus are annoying symptoms frequently encountered. The patient may complain of a tender mass on the anterior part of the vaginal wall and seepage from the urethra. Other symptoms that may be noted are chills, fever, and backache. Occasionally difficulty with urination is a prominent symptom.

CASE REPORTS

Case 1. Mrs. D. E. D., white, No. 120179, aged 31, had 1 child. One month prior to admission she noticed a slight swelling and soreness in the anterior part of the vagina. There was associated frequency and urgency with a nocturia of one time. When nervous and upset, she would be more conscious of something wrong in the area of her vagina, and the neck of the bladder. Intercourse was quite painful. Examination revealed a tender mass in the anterior wall of the vagina. With compression on this mass, pus and urine could be seen oozing from the external urethral meatus. The urethra was catheterized readily, and the catheterized urine was free of infection. Cystoscopic inspection showed the bladder to be within the limits of normal. Examination of the urethra with the panendoscope showed the opening of a diverticulum on the floor of the urethra in its mid portion. Through this opening the diverticulum could be partially inspected. The x-ray (fig. 1) showed the diverticulum filled with the radio opaque medium. Treatment was operative excision with closure of the urethral defect and the incision in the vaginal mucosa. The patient is well and symptom free.

Case 2. Mrs. F. L. J., white, No. 106094, aged 44, had no children. She was admitted to hospital because of difficulty in voiding. She noted also frequency and dysuria and straining to void. There were no symptoms referable to the upper urinary tract. Twelve years previously she was catheterized on a routine examination, and she stated that she had had trouble ever since. On several occasions she had been told that she had pus in her urine, and she had received several bladder irrigations. Two years before admission she had another flare-up of bladder symptoms which responded to bed rest. Two months prior to admission she noted a swelling in the anterior part of the vagina with marked tenderness and a frequency of urination. On examination it was difficult to get a catheter into the bladder, but after it did pass into the bladder, the catheterized urine was free of infection. The urethra was dilated to a 24, and then the cystoscope was passed with ease. The bladder was normal save for slight trabeculation. A firm mass was palpable on the anterior vaginal wall which represents a diverticulum containing a stone (fig. 2). Treatment was surgical excision of the sac with closure of the defect in the urethra and vaginal mucosa. The patient is now well and free of symptoms.

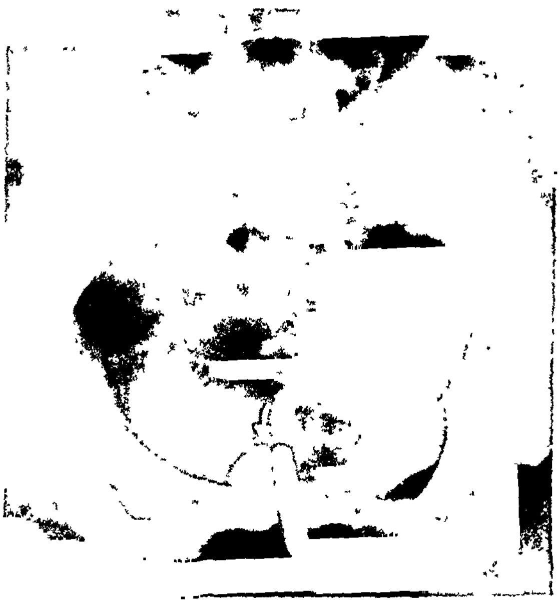

FIG. 1

Case 3. Mrs. E. A. M., white, No. 114425, aged 35, had 3 children. For 3 months prior to admission she had urgency and dysuria. She had no symptoms referable to the upper urinary tract, and there was no history of any mass in the anterior wall of the vagina as far as the patient knew. Examination revealed pus seeping from the urethral meatus after palpation of the urethra. Catheterized urine was negative. Pelvic examination revealed no mass along the urethra. A probe passed into the urethra readily, but promptly dropped into a diverticulum on the posterior floor in the midportion of the urethra. Using the panendoscope, this opening to the diverticulum was readily visualized. This patient was treated the same as the previous case with excellent results, and patient is now well.

Case 4. S. A. H., a colored woman, out-patient department, aged 35 years, complained of frequency and urgency of urination with terminal tenesmus and pain on intercourse. The urine was negative. Examination showed a diverticulum of the urethra, the mass being readily palpable in the anterior wall of the vagina. The patient refused treatment, and she has not been seen since.

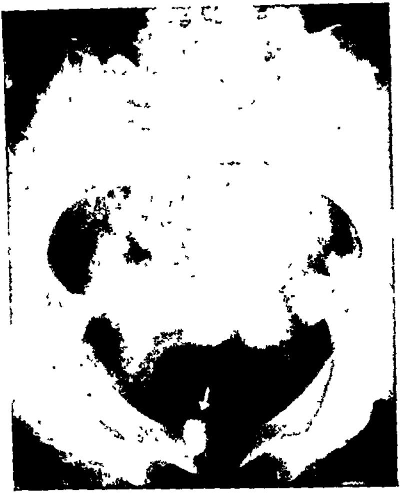

FIG. 2

DISCUSSION

The diagnosis of diverticula of the urethra depends on eliciting a good history and suspecting pathological changes in the urethra. One cannot rely on cystoscopic examination with the right angle lens to make a diagnosis. The urethra must be inspected directly with a suitable endoscope to appreciate the opening of a diverticulum in order to make the diagnosis, because the diverticulum may not always be palpable in the anterior vaginal wall. The fact that the catheterized urine is negative does not rule out urethral lesions. Diverticula may occur at any age, but in any woman in the thirties with bladder symptoms it may be wise to keep this possibility in mind.

It is the authors' belief that the best treatment is total excision with closure of the urethra with two layers of suture followed in turn by closure of the vaginal incision. An indwelling catheter should be left in place from 4 to 5 days for drainage of the bladder. One precaution should be borne in mind: In cases where the diverticulum is of fair size and extends back towards the neck of the bladder and the trigone, in the dissection one may possibly do damage to the bladder sphincter and care should be taken.

CONCLUSIONS

Four cases of diverticulum of the urethra are reported, including one containing a calculus.

Infection in the urine is not necessarily a finding in diverticulum of the urethra.

Diverticulum of the female urethra can easily be overlooked unless one is urethra conscious and makes an adequate study to establish a diagnosis.

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CHRONIC TRICHOMONAS SKENEITIS[1]

LEANDER WILLIAM RIBA

The question of human trichomoniasis has been studied repeatedly for the past 110 years As yet many of its important questions remain unanswered Both clinicians and laboratory investigators have added important bits of information, but the whole sequence of these infections and their recurrences remains obscure.

Many previous investigators such as Allen, Brady and Reid, Karanky, Rakoff, Reich, Schneider, and others, have mentioned the urethra, and Bartholin's as well as Skene's glands as possible chronic primary trichomonas foci of infection Skelanski and Savitz in 1939 reported 11 cases of vaginal trichomoniasis, four of which showed the flagellates in the secretions of Skene's ducts All 11 cases showed the Bartholin gland secretions to be harboring trichomonas (5 in the right, 1 in the left, and 5 in both glands) Hartwell in 1940 was suspicious that the urethra and Skene's ducts could be primary trichomonas foci even though he was unable to demonstrate them in the secretions

The most important factors repeatedly mentioned as the source of recurrent trichomoniasis in the female are. 1) reinfection from the male, 2) reinfection from the rectum, 3) reinfection from the patient's urethra and bladder, 4) reinfection from Bartholin's and Skene's glands The importance or the merits of each of the above factors will not be discussed in this paper Neither will the question, whether or not trichomonas vaginalis causes an infection or an infestation be debated, nor will there be discussion as to whether or not the associated streptococci or other bacteria are primarily responsible for the symptoms The essayist feels that asymptomatic male and female trichomonas carriers do exist Experience indicates that the majority of lesions associated with motile trichomonas vaginalis are imperfectly understood, bonafide infections

The object of this paper is to report the cases of 3 women who had chronic urethral and Skene's trichomonas foci which were associated with a refractory trichomonas vaginitis for 10 months, 12 years and 14 years, respectively The trichomonas were easily demonstrated in the secretions expressed from both Skene's ducts in 2 patients and in the secretions from an aberrant right paraurethral duct in the third patient Eradication of the urethral and Skene's foci caused a clearing of both urinary and vaginal trichomoniasis in 2 patients In the third patient the urinary findings cleared but vaginal trichomoniasis persisted because of an unrecognized left trichomonas Bartholinitis No priority is claimed and the importance of these lesions has been previously reported We were, however, unable to find any specific cases where the destruction of the urethral foci resulted in clinical cure of trichomonas

CASE REPORTS

Case 1 Mrs L H , aged 41, gave a history of vaginal discharge and urinary frequency for 10 months Examinaton showed chronic bilateral skeneitis and granular urethritis The sediment of the urine, the fresh secretions from the right Skene's ducts and the vagina showed pus and many motile trichomonas vaginalis. Palpation of the urethra showed tenderness and a desire to void. In addition there were at least 7 paraurethral ducts. Urethroscopy showed a moderate granular urethritis. The granulations were lightly fulgurated on August 4, 1948, and Skene's ducts were incised with a high frequency current. All the symptoms disappeared. Stripping of the urethra 4 weeks later again showed secretion and motile trichomonas in a paraurethral duct located near the previous right Skene's duct. On September 8, 1948, under anesthesia, 3 additional paraurethral ducts were incised, including the one harboring the trichomonas. The incision of these ducts caused a rapid clearing of the pelvic trichomoniasis.

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[1] Read at annual meeting North Central Section, American Urological Association, Des Moines, Iowa, October 28, 1948

Case 2. Miss M. M., aged 41, complained of marked frequency, urgency and nocturia for 4 weeks. She had been treated for vaginal trichomoniasis by a gynecologist for 12 years. Examination of the urethra showed thickened Skene's glands, the secretion of which showed pus and motile trichomonas. The entire urethra was tender and palpation excited a desire to void. The vaginal secretion showed pus and motile flagellates. The urine was grossly clear and the culture was sterile. The urinary sediment showed epithelial cells, an occasional pus cell and motile trichomonas. On April 15, 1948, urethroscopy showed granulations, polyps and cysts in the deep urethra. These lesions were easily destroyed with a weak electrocoagulation current. The thickened Skene's ducts were incised into the lumen of the urethra. During the next 2 months 3 large sounds were passed into the urethra. On August 9, the patient considered herself entirely well. Examination of the urine and vaginal secretions showed no evidence of trichomoniasis.

Case 3. Mrs G. G., aged 39, complained of pain in the urethra for 6 years and a vaginal discharge for 14 years. One pregnancy in 1941 was delivered by caesarean section. There was a history of pyelitis 3 days after delivery and a second attack 3 years later. Examination showed a thickened tender urethra. Stripping showed that a purulent secretion could be expressed from each Skene's duct. The fresh smears of this material and the urinary sediment showed motile trichomonas. The culture of the urine was sterile. The vaginal smears showed pus and trichomonas. The excretory pyelograms, except for a double left kidney and upper ureter, were normal. Urethroscopy on April 7, 1948 showed deep urethral granulations, grade 2. Inspection of the distal urethra revealed two Skene's ducts on each side. These four ducts were probed and incised into the lumen of the urethra. The urethral granulations were removed by fulguration. The patient felt a great deal better, but a check on September 1, 1948 showed recurrent vaginal trichomoniasis. Re-examination revealed a thickened left Bartholin's gland. Aspiration of the secretion from this gland showed active trichomonas. The gland was irrigated twice with 1 per cent aqueous silver picrate solution and a check-up on October 18 showed no residues of trichomoniasis. The urethra and urine at this time were normal.

DISCUSSION

These case reports are not presented as a panacea for the treatment of female trichomoniasis. They do suggest, however, that the urethra or vagina may be responsible for persistent trichomonas foci. The eradication of these foci will aid in clearing these chronic infections. All factors carefully considered, our experiences indicate that all vaginal and paraurethral ducts and glands should be suspected in resistant female trichomoniasis. The secretions from these structures, mixed with normal saline solution should be examined immediately under the highpower microscope. The flagellates are easily identified when they are present. Repeated fresh secretion examinations may be necessary for establishing the final diagnosis. The Bartholin's gland secretions may be aspirated with a suction cannula. The secretions from the paraurethral ducts are easily expressed by stripping and picked up with a wire loop or a glass pipette.

Our treatments have been carried out in the hospital under sodium pentothal or low spinal anesthesia. The bladder, trigone and entire urethra are carefully examined. All the lesions noted in the deep urethra are treated with a weak electrocoagulation current through a water endoscope. These deep urethral granulations polyps or cysts may possibly be related to the trichomoniasis. The paraurethral ducts are catheterized with a semiflexible electrode and incised into the lumen of the distal urethra with a high frequency cutting current. We have found it difficult to recognize all of the offending paraurethral ducts which may be present. Anomalous ducts are exceedingly common and predispose to residual post-treatment foci. Co-existing chronic Bartholin trichomonas foci should be treated by irrigation, drainage or excision. Chemotherapy or antibiotics are used when the urine is infected. After 3 or 4 weeks the urethra is dilated periodically to its maximum caliber. As soon as possible, in addition, vaginal treatments are recommended.

Trichomonas vaginalis may be present in the male or female without any symptoms or evidence of infection. The husbands of these patients should be examined for trichomonas. Anterior urethral strictures predispose to male trichomoniasis. Advice regarding vaginal and rectal hygiene is helpful.

CONCLUSIONS

Two cases of chronic female trichomoniasis were clinically cured by eradicating the urethral and paraurethral foci. In addition to all other known factors, these foci should be considered in resistant trichomonas infections. One failure resulted from an unrecognized trichomonas Bartholinitis. Belated irrigation of this gland with 1 per cent silver picrate solution caused a clearing of the residual focus.

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PRIMARY CARCINOMA OF THE MALE URETHRA: REPORT OF TWO CASES

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Primary carcinoma of the male urethra is a rare urogenital lesion. In 1939 Kreutzmann and Colloff, reviewing the literature, collected 148 cases and reported 2 additional ones. A recent article by Lower and Hausfield reported 192 cases recorded in the literature to January 1946. This included the 10 cases they report seen at the Cleveland Clinic over the period extending from 1908. Zaslow and Priestley in 1947 reported that 25 cases of primary urethral neoplasm were seen at the Mayo Clinic in the 35 year period from 1910 to 1945 inclusive. In the experience of the average practicing urologist, therefore, the incidence of this lesion is rare indeed. Two cases of primary carcinoma of the male urethra recently treated on the Urological Service of the York Hospital prompted this report. These are the only cases of primary neoplasm of the male urethra seen at the hospital in 105,257 admissions.

CASE REPORTS

Case 1. A 42 year old white man was admitted to the York Hospital June 13, 1948 for investigation of persistent urethral stricture and multiple perineal sinuses. Progressive difficulty in voiding for the past 3 years was relieved by interval dilatation of urethral strictures by his local physician. In December 1947 more frequent dilatation became necessary and several months before admission he noted perineal swelling and the subsequent development of multiple draining perineal sinuses. There was a history of gonorrhea 20 years previously.

On June 14, 1948, under pentothal anesthesia, the urethral stricture in the bulbomembranous portion was dilated with filiforms and followers and a 5 cc Foley catheter inserted. At this time the perineum was incised and drained, the sinus tracts curetted and packed with gauze. The Foley catheter was removed on the fourth postoperative day and following its removal the patient voided voluntarily, about one half the urine passing through the external meatus and the remainder through the perineal sinuses. The patient was discharged June 20, 1948. Subsequently there was continuous discharge of purulent material through the perineal sinuses and on voiding most of the urine escaped through these fistulous tracts. He was re admitted August 2, 1948 for further observation and treatment.

On re admission he appeared cachectic and had lost about 20 pounds. Physical examination revealed an emaciated man who appeared chronically ill. The head and neck were negative, the heart was not enlarged, no abnormalities of rate or rhythm. The blood pressure was 140/70. The abdomen was soft, no masses present, liver, spleen and kidneys were not palpable. Moderate enlargement of the inguinal lymph nodes was noted. Examination of the genitalia revealed marked perineal induration and swelling and several sinus tract openings in this region. The orifice of one of these was surrounded with built up granulation tissue which appeared malignant.

The urine was grossly infected and all was passing through the perineal sinuses. and there was continuous discharge of foul smelling purulent material. Laboratory study showed red blood cells 3,900,000; hemoglobin 10.6; white blood cells 20,100. A Foley catheter was again inserted and several sections removed from the sinus tract and orifice for microscopic study. Dr. L. C. Pusch, pathologist of York Hospital, reported squamous cell carcinoma, grade 2, of the urethra (fig. 1, *A*).

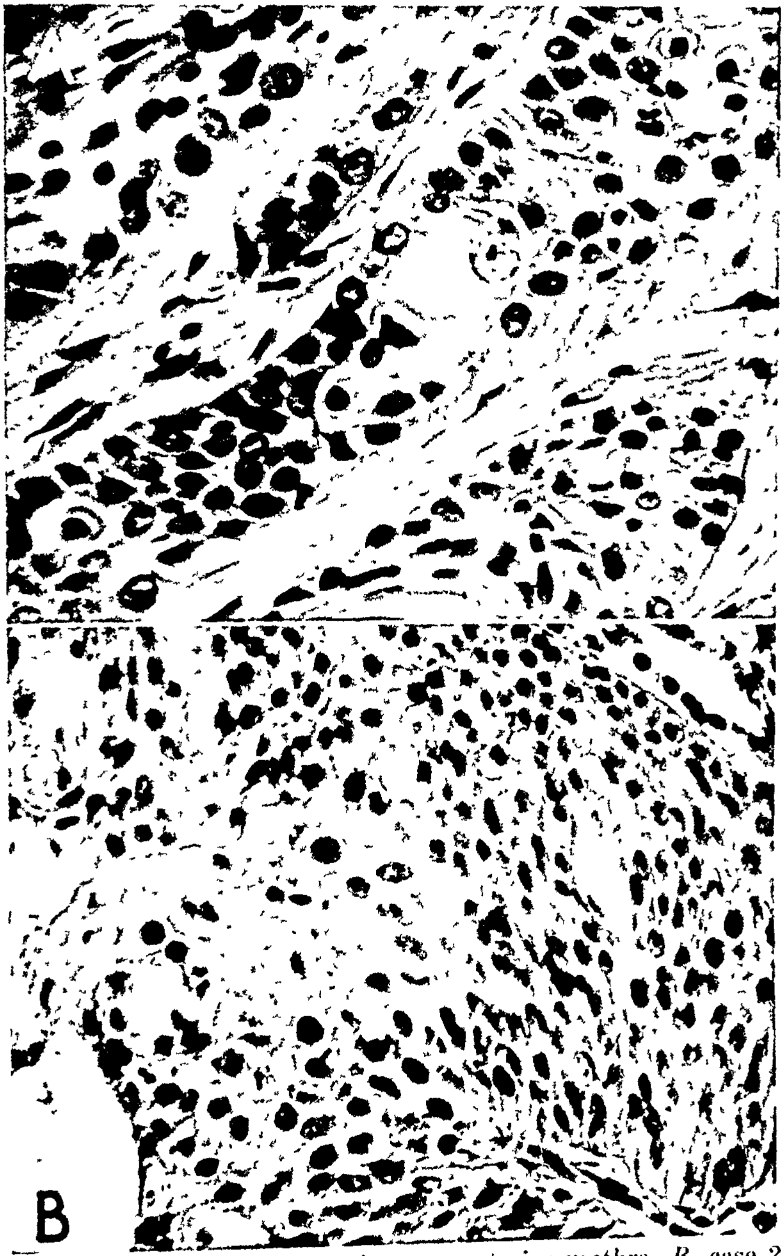

Fig. I. *A*, case I. Squamous cell carcinoma, posterior urethra. *B*, case 2. Squamous cell carcinoma, fossa navicularis.

The clinical course was progressively downhill. The patient had a low grade intermittent fever in spite of penicillin and supportive therapy. Sepsis and cachexia increased and the patient expired August 20, 1948.

On postmortem examination the perineum was indurated and on the right side, situated anteriorly to the anal orifice, was a large confluent sinus opening. The lungs revealed only hypostatic congestion. No gross evidence of metastases to liver, kidneys and spleen was present. The gastro-intestinal tract, biliary tract, pancreas and adrenal glands were essentially normal. Microscopic section of organ systems enumerated showed no evidence metastases.

The bladder wall was thickened; the inner lining was trabeculated and hemorrhagic. The vesical neck, prostatic urethra, and the distal portion of the membraneous urethra throughout an aggregrate length of 5 cm. was replaced by friable, whitish tissue 1 to 1.5 cm. in thickness with the lumen of the urethra communicating with the cutaneous surface of the perineum through a large sinus opening. Microscopic section of the primary urethral neoplasm revealed squamous cell carcinoma identical with the biopsy specimen. Sections of inguinal nodes revealed an inflammatory lymphadenitis. There was no evidence of metastases microscopically in the regional lymph nodes.

Case 2. A 26 year old man was first seen by his family physician November 1, 1948 with the complaint of a small warty growth present at the external urinary meatus. The patient noted its appearance 3 weeks prior to presenting for treatment. He denied hematuria or urinary symptoms of any type. There was no history of gonorrhea. The small, warty like growth was fulgurated as an office procedure and a biopsy specimen sent for pathological study. Dr. L. C. Pusch reported squamous cell carcinoma, grade 1 (fig. 1, *B*) "the specimen consisting almost entirely of bulky, anastomasing columns of well differentiated squamous epidermal cells, hyperchromatic and mitotic nuclei are readily found and macronucleoli are prominent."

The patient was referred by his family physician for urological opinion following receipt of the biopsy report. He was first seen in consultation November 24. Initial examination revealed a well developed, well nourished white man; head and neck negative; chest clear and breath sounds normal. The cardiac rate was regular, the tones of good quality, no murmurs, blood pressure 120/80. The abdomen was soft, no masses were present, liver and spleen not palpable. No inguinal adenopathy was present. Genitalia presented normal scrotal and adenexal contents. Examination of the penis revealed no induration of penile urethra; at the meatus, situated in the center of the fossa navicularis, was a small, residual warty-like excrescence measuring 3 mm. in diameter. The surrounding mucous membrane was smooth with no evidence of infiltration or induration. The lesion appeared confined to the fossa with no extension to the penile urethra.

On November 30, under sodium pentothal anesthesia, the fossa navicularis was excised en bloc including a wide margin of tissue on all sides of the small residual lesion. The edges and base of the excised bloc were thoroughly fulgurated using the ball tip electrode. Examination of the excised specimen by Dr. L. C. Pusch revealed the lesion to have been completely excised and "the proliferating cells nowhere approaching the margin of the specimen."

The area healed uneventfully. Progress dilatations have been carried out to prevent stricture formation at the meatus. Progress urethroscopy 6 weeks following the procedure revealed the urethra throughout its length to be normal in appearance. The necessity of careful periodic follow-up has been emphasized to this patient.

ETIOLOGICAL FACTORS

Most authors are in agreement that the presence of old stricture or long continued urethral irritation precedes the development of the malignancy in many instances. Goldstein and Abeshouse list the following as possible predisposing factors: a) nonspecific urethritis; b) gonorrhea and its complications; c) papilloma or polyp formation; d) leukoplakia; e) trauma or irritation of a chemical nature; f) sex perversion; g) sexual contact; h) Paget's disease of the penis.

In our cases the history of stricture was elicited in one instance; the other patient presented no evidence of stricture, denied venereal disease or preexistant urethral irritation.

LOCATION

Carcinoma may arise in any portion of the urethra. From the reported cases it would appear that the posterior segment is more frequently involved than the anterior urethra. Kreutzmann and Colloff report that in 60 of 143 cases studied, the lesion was located in the anterior urethra, and 73 occurred in the posterior portion. In our cases one involved the anterior (fossa navicularis), the other the posterior urethra. Lesions arising in the fossa navicularis are uncommon. Perez in 1945 reviewed the literature and recorded 28 such cases arising in the fossa and reported an additional case. Zaslow and Priestley in 1947 found 5 additional such cases in the literature in preparing their review.

PATHOLOGY

The histopathology of the vast majority of these tumors arising from the squamous and transitional epithelium of the male urethra are of the squamous cell type. Kreutzmann and Colloff summarize the pathologic type and incidence of their collected series as follows:

	cases
Squamous cell carcinoma or epithelioma	101
Papillary carcinoma	6
Transitional cell carcinoma	3
Adenocarcinoma	2
Mucoid gland carcinoma	2
Columnar cell carcinoma	1
Endothelioma	1

Our cases both represented the squamous cell variety: one arising in the anterior urethra (fossa navicularis), the other in the posterior prostatic segment. Harbach speculates that the occurrence of squamous cell carcinoma arising in portions of the urethra not normally lined by the presence of squamous epithelium may be accounted for either by a metaplasia or by embryonal cell inclusions. He points out that old strictures tend to develop nests of squamous epithelium, probably a metaplasia due to infection and irritation. This would seem in accord with the general opinion that preceding stricture or chronic irritation act as predisposing factors in the development of this lesion in many instances

METASTASES

For the most part these neoplasms are of rather low grade malignancy, metastasizing slowly to the inguinal or iliac nodes by way of the regional lymphatics From these regional nodes dissemination by the blood stream may spread the growth to distant sites Metastases in lung and liver have been reported At autopsy our case presented involvement of the posterior urethra with perineal sinus formation by direct extension There were no metastases to the regional nodes or distant organs

SYMPTOMS AND DIAGNOSIS

As in any lesion involving the lower urogenital tract, the symptoms may be protean depending upon its location and degree of interference with lower urinary tract function The high incidence of antecedent stricture and irritative precursors renders no symptom complex pathognomonic of early malignancy.

The most commonly reported symptoms are hematuria, recurrent penile discharge, and dysuria In numerous instances urinary obstruction and fistulous formation secondary to widespread infiltration of the neoplasm have been the factors bringing the patient to seek medical aid Carcinoma of the urethra must be kept in mind when dealing with any persistent stricture which does not respond to therapy in the usual fashion or which is associated with recurrent bleeding and, as emphasized by Goldstein and Abeshouse, repeated urethroscopic examination of the lower urinary tract is indicated in such cases in which cystoscopy does not reveal the exact cause of the difficulty Biopsy and careful pathological study of all polypi and papillomata removed or fulgurated at the fossa navicularis or anterior urethra is mandatory so that early lesions amenable to therapy may be discovered and completely eradicated

TREATMENT

In any neoplasm the hope of cure is based upon complete extirpation of the lesion Unfortunately in many cases the diagnosis is made late when widespread local infiltration, extension or metastases renders this procedure difficult or impossible The method must be individualized, dependent upon the location, and extent of the process at the time of diagnosis Zaslow and Priestley in their series of 25 cases report that for relatively small growths in the fossa navicularis radium may be applied directly or fulguration may be used to destroy a small lesion In the penile urethra, amputation, radium and fulguration were utilized In the posterior channel prostatectomy, cauterization, radium, transurethral removal and fulguration were used Hugh H Young in 1939 reported a method of radical operation for removal of the bulbous portion of the urethra which would appear ideal in selected cases in the hands of one experienced in perineal surgery Inguinal gland dissection has been advised in conjunction with amputation or bloc dissection when the nodes are involved Unfortunately in many

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CONGENITAL EPISPADIAS WITH INCONTINENCE[1]

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The purpose of this paper is to plead for the use of reconstructive plastic surgery in the treatment of the urinary incontinence and genital defects associated with congenital epispadias. It is felt that uretero enterostomy is rarely indicated in the treatment of this condition and, if used at all, should be employed as a procedure of last resort.

Congenital epispadias in the male is characterized by the abnormal location of the urethral opening on the dorsum of the penis. The opening may be situated anywhere between the glans penis and the penopubic junction. Depending upon its location, epispadias is classified as balanic, penile, or penopubic, the latter being by far the most common condition. Penopubic, or complete epispadias is usually associated with absolute incontinence of urine due to a congenital lack of fusion of the internal and external urethral sphincters ventrally. The urethra is usually of such large caliber that it will easily admit the examiner's index finger. The symphysis pubis is characteristically separated, there being a heavy band of fibrous tissue joining the separated halves. The penis is of normal size and drawn acutely upward against the abdominal wall. The prepuce is redundant on the ventrum of the penis and lacking on its dorsum. The corpus spongiosum is rudimentary or absent and the corpora cavernosa are loosely attached to each other. The glans penis exhibits a defect or groove along its dorsal suface which is continuous along the dorsum of the penis with a mucous membrane lined depression between the corpora cavernosa. This trough is continuous proximally with an infundibulum or funnel-shaped opening which extends inward beneath the symphysis pubis to become continuous with the prostatic urethra. The power of erection is usually present but coitus is virtually impossible. The bladder itself is usually normal except for the internal vesical sphincter which is widely dilated so that the interior of the bladder and prostatic urethra form a continuous pear shaped cavity.

Analogous defects occur in the external genitalia of the female. Absolute incontinence of urine is the rule. The labia majora are separated anteriorly. Between their anterior portions and extending up over the symphysis is an expanse of skin devoid of hair in the adult. The labia minora are separated anteriorly and the clitoris is bifid. As in the male, the urethra is patulous and the bladder normal except for incompetence of the internal vesical sphincter. The vagina and internal genitalia are usually normal.

Fortunately, epispadias is one of the rarest of all congenital anomalies and for this reason, relatively few articles discussing its treatment have appeared in the medical literature. To the individual so afflicted, however, the condition is tragic as the continuously wet clothing and uriniferous odor usually bring about social ostracism. The deformity of the genitalia, besides causing deep-seated psychic trauma, virtually prohibits normal sexual activity.

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[1] Read at a meeting of the Detroit Urological Association, Detroit, Mich., September 21, 1948.

In an effort to determine the incidence of this anomaly, a recent survey has been made of several of the larger hospitals in this country (table 1). Among a total of 5,292,212 patients indexed in the diagnostic files of these hospitals, there were 45 cases of congenital epispadias with incontinence in males and 11 in females. This gives an incidence of 1 male case of epispadias with incontinence in 117,604 and 1 female in 481,110. These records have not been reviewed personally for verification of the diagnosis but it seems probable that the above incidence is approximately correct.

In 1942, I reported the cure, by plastic operation upon the bladder neck and urethra, of 2 cases of epispadias with urinary incontinence in the male. Three additional cases in the male, 1 with, and 2 without urinary incontinence had been seen but not operated upon. Since then, 3 additional cases in males and 1 case in a female have been seen and operated upon. In all of these, excellent control of urination, and, from an anatomical standpoint, relatively normal external genitalia have resulted.

TABLE 1. *Incidence of congenital epispadias with incontinence*

HOSPITAL	NO. OF PATIENTS INDEXED	MALE	FEMALE
Johns Hopkins	316,622	12	3
New York	165,977	9	4
Charity (New Orleans)	2,628,113	5	0
Boston City	148,233	3	1
Philadelphia General	265,325	1	0
University of Virginia	207,110	1	2
Los Angeles County	919,361	8	0
Duke	341,471	6	1
Total	5,292,212	45	11

1 male case in 117,604.
1 female case in 481,110.

The embryological explanation for the occurrence of epispadias as well as the history of the development of various operative procedures for its correction have been reviewed in a previous article. The surgical procedure used in most of these cases has been a modification of Young's double sphincter operation which was described in 1922. This procedure, as modified, consists first of suprapubic exposure of the bladder (fig. 1). The anterior and lateral aspects of the prostate (or the urethra in the female) are freed as much as possible from the dorsal surface of the intersymphyseal band. The bladder is then opened along the midline from its dome to the level of the external sphincter dividing the roof of the posterior urethra as the incision is continued downward. A triangular wedge of tissue is then excised from the roof and each lateral wall of the posterior urethra and adjacent bladder wall including a portion of each lateral lobe of the prostate in the male. It is important that the incisions through each side of the floor of the posterior urethra be parallel and placed 6 to 8 cm. apart. Subsequent closure results in a snug internal and external sphincter and a tubular, rather than conical, urethra. Because of the close proximity of the vagina to the bladder wall in the female, it is preferable to excise a somewhat smaller wedge of bladder wall and urethra than is removed in the male. The bladder wall immediately on each side of the central strip of mucous membrane (which will ultimately form the new urethra) is then denuded of its mucosa (fig. 2). Not only is the risk of accidental injury to the vagina lessened, but utilization of the thick musculature

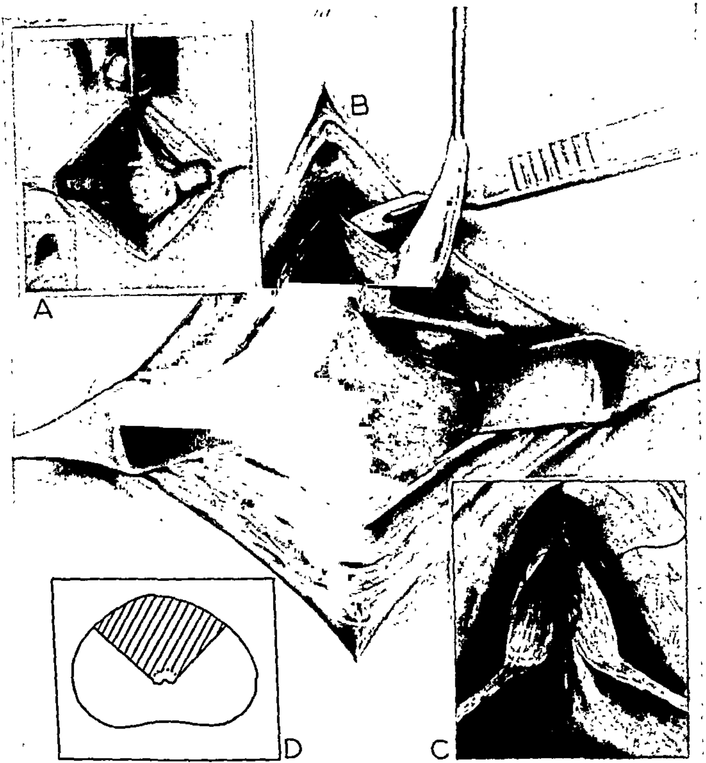

Fig. 1. *A*, Young's technique for resection of wedge from vesical neck and prostatic urethra. *B*, bladder and prostatic urethra opened along midline to membranous urethra, resection of triangular piece of tissue from roof and right lateral lobe of prostate and adjacent bladder; cut edges of floor of prostatic urethra are parallel and closure results in snug internal sphincter and tubular, rather than conical urethra; corresponding tissue is excised from left side as indicated in illustration. *C*, closure results in tubular urethra, tight internal sphincter; second layer of plicating sutures to be introduced. *D*, cross section of prostate shows preservation of only floor of urethra but of most of lateral prostatic lobes by oblique incisions. (Republished from ref. 1 by permission of the C. V. Mosby Co., publishers of *Surgery*.)

of trigone and bladder wall greatly facilitates closure of the new urethra and, I believe, aids in establishing urinary control. The urethra is constructed over a small 8 or 10 F rubber catheter by means of a continuous chromic catgut suture which commences at the level of the external sphincter region and continues upward to close the bladder around a mushroom catheter. A second similar suture is placed to reinforce and plicate the initial line of closure.

At a second stage in the male, the roof and lateral walls of the distal portion of the urethra are excised from below, the mucosa of the floor being preserved to line the new urethra. The raw tissues lateral to the remaining urethral mucosa are then approximated over a small catheter. The penile urethra is constructed from the mucous membrane which lines the groove along the dorsum of the penis The corpora cavernosa are separated and the newly constructed urethra displaced to its proper position on the under surface of the penis and held there by re-approximating the corpora dorsal to it. An appropriate amount of excess skin is resected from the dorsum of the shaft and glans of the penis and the skin edges approximated in the midline by interrupted sutures. In the female (fig. 3) 2 diverging incisions are made with their apex in the presymphyseal region Each diverging limb follows the medial aspect of the separated labia majora denuding the inner aspect of each half of the bifid clitoris. The incisions are then directed medially to excise the lateral walls and roof of the urethra. The adjacent urethral musculature is approximated in front of a small catheter lying on the

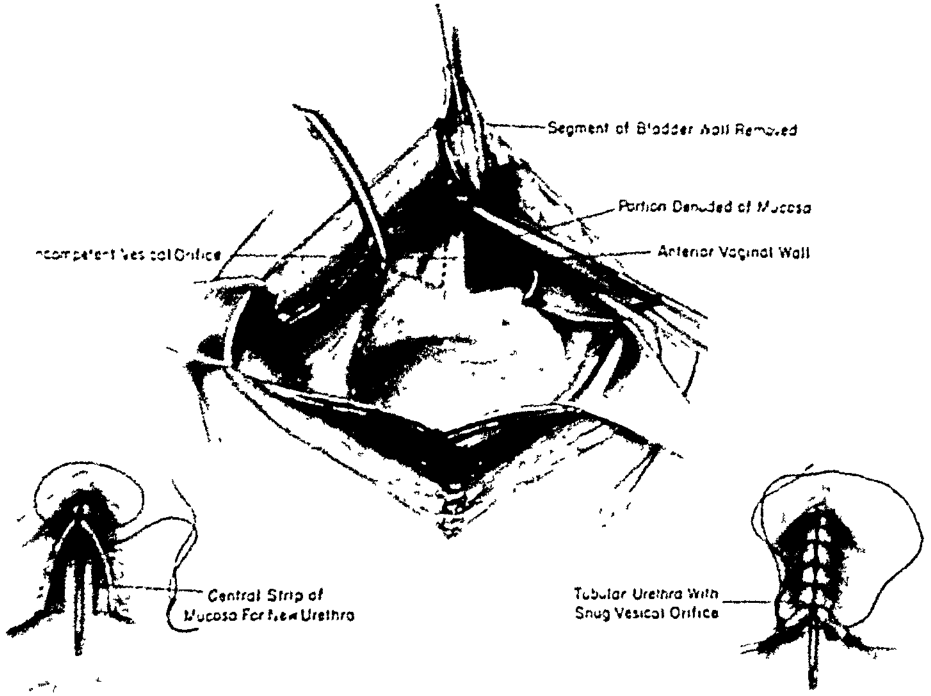
Segment of Bladder Wall Removed
Portion Denuded of Mucosa
Incompetent Vesical Orifice
Anterior Vaginal Wall
Central Strip of Mucosa For New Urethra
Tubular Urethra With Snug Vesical Orifice

FIG. 2. Plastic on vesical orifice in female. Resection of triangular segment of bladder wall and trigone from each side of urethra and vesical orifice. Preservation of portion of trigonal and vesical musculature denuded of mucosa on each side of midline to avoid injury to vagina and to aid in urethral reconstruction.

mucosa of the urethral floor. Closure of the skin approximates the anterior portions of the labia majora and the halves of the bifid clitoris.

CASE REPORTS

Case 1. No. 59615. H.R.S. (fig. 4, *A* and *B*) a 14 year old white boy had complete incontinence of urine since birth due to congenital penopubic epispadias. The first stage of Young's double sphincter operation was carried out on October 23, and the second stage on December 2, 1935, by Dr. E. P. Alyea. Per primam healing occurred and complete urinary control resulted. When last heard from 13 years after operation, the patient was doing heavy manual labor and urinary control was perfect. He was the father of 2 healthy children and the husband of a contented wife.

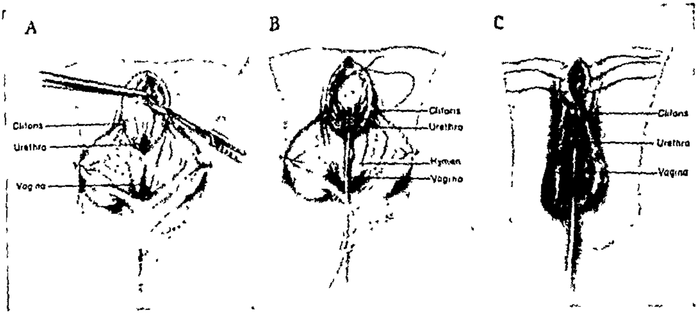

FIG. 3. Plastic on external genitalia in female. Excision of skin and subcutaneous tissue between separated labia and halves of bifid clitoris together with roof and lateral walls of distal urethra. Closure approximates bifid clitoris and labia and tightens distal urethra.

Case 2. No. A 57641. J.E.B. (fig. 4, *C* and *D*), a 15 year old white boy had complete urinary incontinence since birth secondary to congenital penopubic epispadias. The first stage of a modified Young's double sphincter operation was carried out on March 17, and the second stage on April 24, 1941 (J.E.D.). Per primam healing of both operations occurred with establishment of complete urinary control. When last seen 5 months after discharge, there was perfect urinary control except for very occasional enuresis. Urine could be retained for more than 4 hours. Erections were frequent but intercourse or masturbation had not been attempted. The urine was normal and the urethra accommodated a 16 F sound.

Case 3. No. B 11707. H.G.G. (fig. 5, *A* and *B*), a 13 year old white boy, had partial urinary incontinence secondary to penopubic epispadias since birth. There was no enuresis, but frequent diurnal incontinence. The first stage of a modified Young's double sphincter operation was performed by Dr. E. P. Alyea on August 18, 1943 and the second stage on November 10, 1943. Perfect urinary control was established but a small penile urinary fistula resulted which, after two unsuccessful attempts, was finally closed on April 17, 1946. Four months ater, he was completely healed and urinary control was perfect. The urine was ormal and there were no urinary symptoms.

Case 4. No. C 22229. K.C.L. (fig. 5, *C* and *D*), a 4 year old boy had complete rinary incontinence secondary to congenital penopubic epispadias since birth.

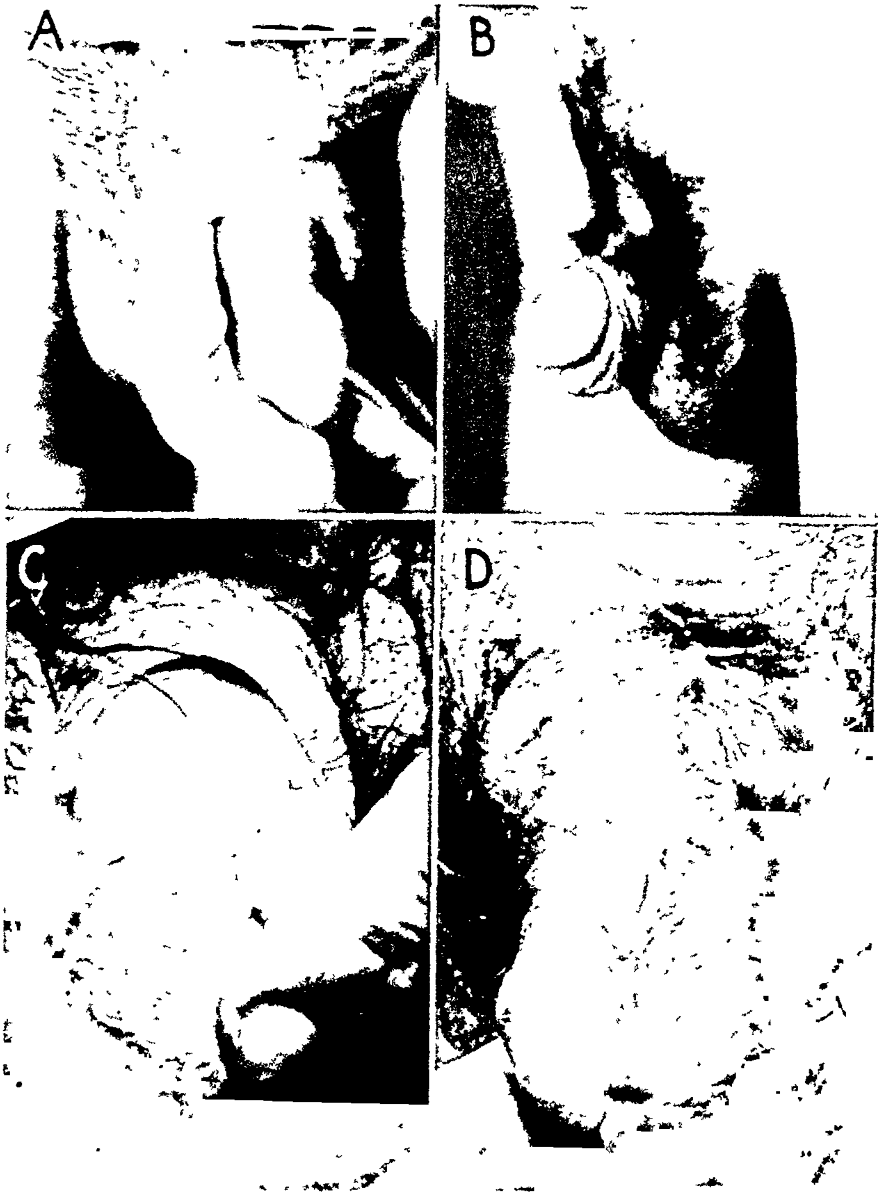

FIG. 4. *A*, case 1. Preoperative view. *B*, postoperative. *C*, case 2. Preoperative view. *B*, postoperative.

The first stage of a modified Young's double sphincter operation for epispadias was carried out on October 24, 1948 (J.E.D.). Although per primam healing resulted, urinary control was only slightly improved, the patient being able to retain urine for no more than 15 minutes. The second stage with construction of the urethra and plication of the external sphincter was carried out on June 30, 1948 When last seen 4 months after his last operation, he could sleep for 5 to 6 hours at night without wetting his bed Occasionally, he could go for 24 hours without incontinence Usually urinary control was perfect in the day until early evening, after which time he would frequently wet himself Both his parents and I believe that his problem now is simply one of training and that complete control will probably be established

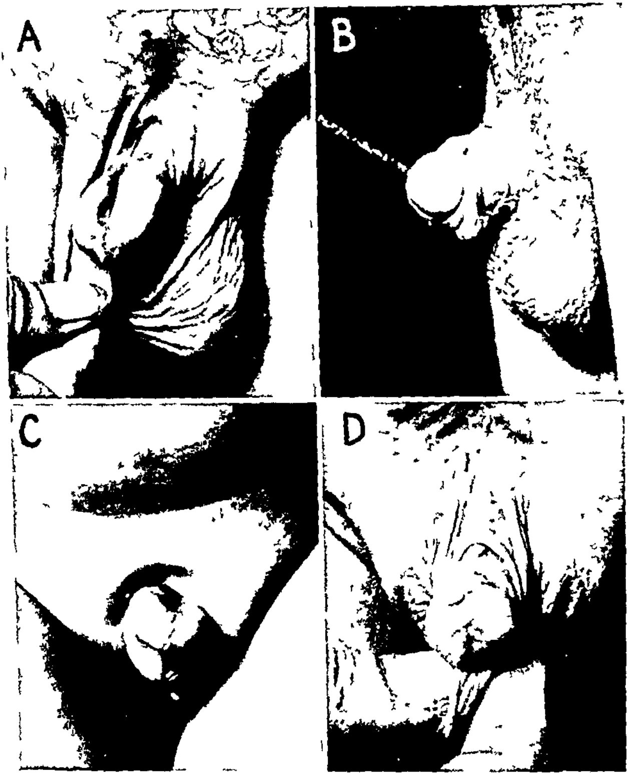

FIG 5 *A*, case 3 Preoperative view *B*, postoperative ,*C* case 4 Preoperative view *D*, postoperative

Case 5 No C 16423, S G B (fig 6, *A* and *B*), a 3 year old white boy, had had partial urinary incontinence since birth secondary to penopubic epispadias There was constant enuresis and complete incontinence if he tried to retain urine for more than a hour or two during the day The second stage of Young's double sphincter operation for epispadias was carried out on November 14, 1947 with establishment of perfect urinary control (J E D) Three small fistulas occurred in the newly formed urethra. These were closed at a second operation on June 30, 1948. When last seen, 4 months after his last operation, a single drop of urine escaped from one of the fistulas during voiding, the other fistulas being

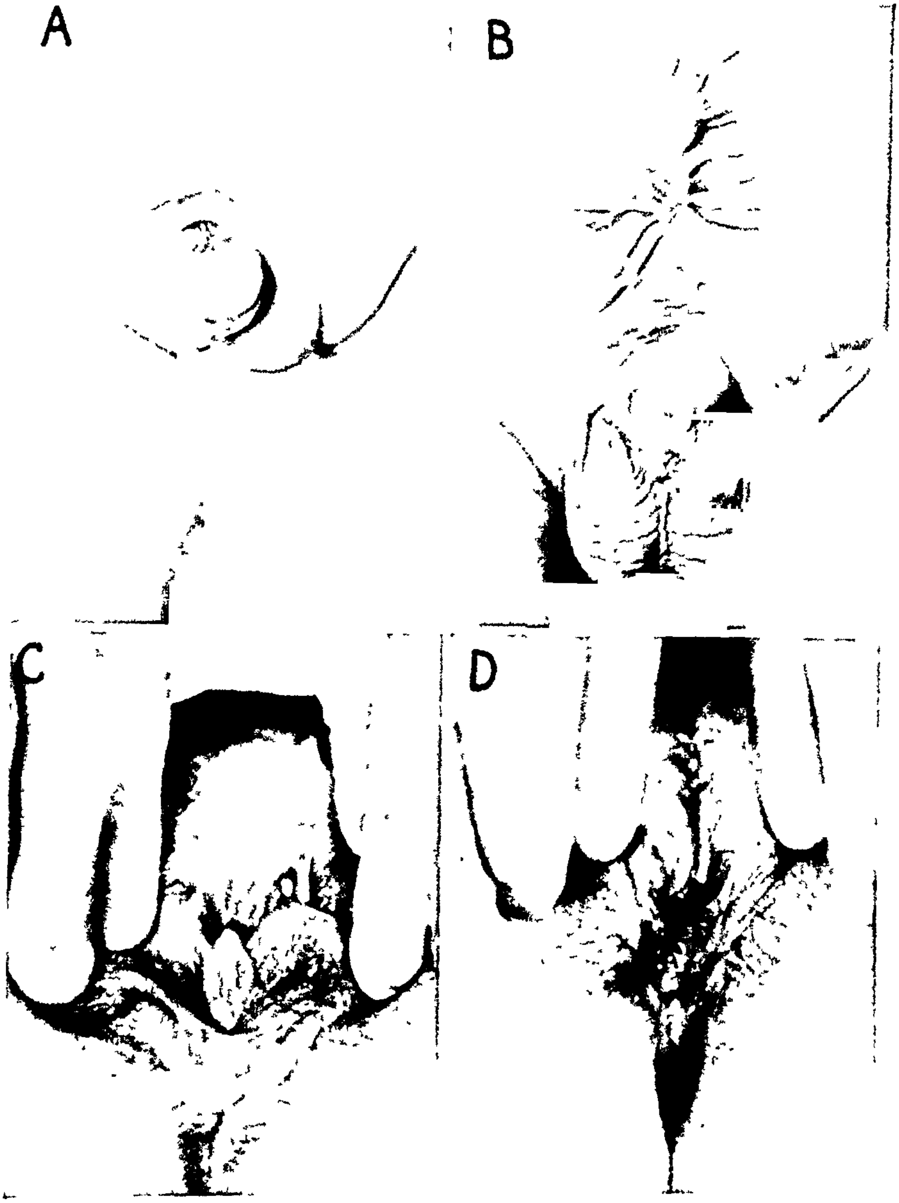

FIG. 6. *A*, case 5. Preoperative view. *B*, postoperative. *C*, case 6. Preoperative. *D*, postoperative.

healed. About once a day while playing, he would wet himself, but control otherwise was perfect. The urine was negative. A perfect result is anticipated.

Because of the extreme rarity of congenital epispadias with incontinence in the female, (an incidence of about 1 in 500,000) the following case is reported in detail.

Case 6. No. C 36980. J.S., a 14 year old white girl, was first seen at Duke Hospital on June 15, 1948. She complained of absolute incontinence of urine since birth, the drainage having been managed by the frequent change of perineal pads At no time had she had any desire to void and the urine escaped in a steady trickle regardless of posture There was no sudden gush of urine when arising from bed in the morning She had had no serious illness nor any symptom suggesting upper urinary tract infection Physical examination revealed a perfectly normal post pubescent girl except for the external genitalia (fig 6, *C*), which showed the classical findings of congenital epispadias The vagina was 9 cm in length, the cervix nulliparous, the corpus uteri anterior and of normal size The adnexal regions were normal Subsequently, under anesthesia, the examiner's index finger could be passed into the bladder through the urethra All accessory clinical findings including urinalyses were within normal limits On June 18, 1948, the bladder was opened suprapubically and the previously described operation, (fig 2), carried out to construct a competent internal sphincter and urethra Her convalescence was uneventful Twelve days later, a plastic operation on the external genitalia and distal urethra (figure 3) was performed with the excision of the presymphyseal skin, approximation of the labia majora anteriorly approximation of the bifid clitoris, and partial resection and plication of the distal urethra An excellent cosmetic result was obtained (fig 6, *D*) On the twelfth postoperative day, the suprapubic catheter was removed and within 24 hours, urethral voiding was established and suprapubic urinary drainage rapidly ceased At the time of discharge, 3 weeks after the second operation, she had perfect urinary control and was voiding at intervals of 3 to 4 hours in quantities as much as 300 cc at a time At her last examination 4 months after operation, urinary control was perfect There was nocturia 1 to 2 times and she was voiding in quantities of 300 cc at intervals of 2 to 3 hours during the day

SUMMARY AND CONCLUSIONS

In all of the 6 cases of epispadias with incontinence herein reported, good or perfect urinary control was established by means of plastic operation on the bladder neck, external sphincter and urethra In 1940, Young reported 13 cases of epispadias with incontinence upon whom he had operated with creation of complete urinary control in 12 and almost perfect control in the other Muschat, in 1927, reported 3 such cases with complete cure Other cures have been reported by Cecil, Lowsley and Kirwin, Hinman, and others As with many operations, failures are reported less frequently than successful results However, if plastic operation on cases of epispadias with incontinence is successful, these individuals are restored to a completely normal social state and a practically normal physical condition Coitus is usually entirely satisfactory, moderate upward curvature of the penis being much less of a handicap than a corresponding degree of ventral chordee Urinary tract infection, if present, presents no different therapeutic problem than it does in a normal individual (In 5 of the 6 cases herein reported, the urine has been uninfected when the patients were last seen) The upper urinary tract has not been disturbed and the life expectancy of the individual should not differ from the average at his age This cannot be said of the condition following uretero-enterostomy, where chronic renal infection or obstruction is not uncommon. The great value of transplanation of the ureters to the bowel is unquestioned in certain conditions, otherwise incurable at the present time, such as exstrophy of the bladder, vesical carcinoma and large vesicovaginal fistulas. In epispadias with incontinence, however, where the abnormality is curable in a high percentage of cases by plastic operation, it is felt that the advantages of the operation described herein so far outweigh those uretero-enterostomy that the latter operation should be reserved as a procedure of last resort.

Acknowledgment: I wish to thank my associate, Dr. Edwin P. Alyea, for his permission to include in this report, the cases of epispadias with incontinence upon whom he so successfully operated.

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TRAUMATIC AVULSION OF THE SKIN OF PENIS AND SCROTUM[1]

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This terrifying accident, avulsion of the skin of the penis and scrotum, is being encountered with increasing frequency. Because of this, it was thought well to consider briefly a few articles published in the last half dozen years and to review the cases most recently recorded at the Mayo Clinic. It was thought that such a recapitulation would bring out the principles on which treatment has been based and it was hoped that description of some new points in technique would emerge.

CONSIDERATION BASED ON 14 CASES

The 14 cases particularly considered herein were encountered at the Mayo Clinic from 1938 to 1947 inclusive. Cases 7, 8, 9 and 12 of table 1 were reported by Judd and Havens, as their cases 5, 8, 9 and 6 respectively. Nielson, Logan and Ferris, moreover, previously have reported case 13 of table 1.

Cause of injury.—In one of the 14 cases the injury took place at birth. In the other 13 cases, the force that caused the avulsion was exerted by farm machinery. The usual history was that the patient's overalls had been caught in the power take-off of a tractor and, before the motor could be stopped, the clothing had engaged the pubic hair and avulsion of the skin had followed immediately. Avulsion of the skin of the penis usually was complete but in only 3 cases did complete avulsion of the scrotum occur.

Restoration of penis.—In cases 11 and 13 (table 1), loss of the penile skin was incomplete and, by a careful plastic procedure, sufficient skin was mobilized to cover the denuded organ. In both cases, the resulting scar underwent slight contracture. All skin was lost in the remaining cases. In each of these, a split-skin graft of medium thickness, obtained by use of a Padgett dermatome, was applied to the shaft of the penis. Results were excellent in all.

Three points in technique should be emphasized:

1. Often a small cuff of foreskin is left intact. In such a case, the surgeon is strongly tempted to pull the cuff down over the shaft as far as possible and then to cover the remaining defect with a graft. This may be a serious mistake because lymphedema may occur in this cuff of foreskin and a doughnut-shaped enlargement may result. In case 5 (table 1) the edematous foreskin had to be removed and a skin graft applied to the area (fig. 1).
2. The surgeon may think it good practice to place the graft so that its edges will meet in the midline, on the urethral surface of the shaft, thus simulating the normal median raphe. It is far better, however, to have this line of scar tissue on the dorsum of the penis because then any contracture of the scar will accentuate the normal curvature of the penis in erection rather than causing curvature in the opposite direction.

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[1] Read at meeting of North Central Section, American Urological Association, Des Moines, Iowa, October 29, 1948.

3. An adequate pressure dressing is needed. The sponge rubber "doughnut" and many other devices have been employed but the contrivance used recently in this series has worked best of all. After the graft has been applied, sterile mechanic's cotton waste is teased out carefully to avoid matting and is then applied evenly around the penis. Pressure is established by building a wire fence around the waste (fig. 2). A urethral catheter is accurately placed and the penis is held at a right angle to the body by a suture placed in the glans and tied to a wooden tongue depressor which is attached to the top of the fence.

TABLE 1. *Traumatic avulsion of the skin of penis and scrotum*

CASE	EXTENT OF INJURY	RESULT OF TREATMENT		REMARKS
		Penis	Scrotum	
1	Scrotum		Excellent	
2	Penis, scrotum	Excellent	Poor	Skin graft on scrotum only 80% take; considerable scarring
3	Penis, scrotum	Excellent	Excellent	
4	Penis, scrotum	Excellent	Good	Testes still in inguinal region
5	Penis, scrotum	Excellent	Excellent	
6	Penis, scrotum	Excellent	Good	Testes still in inguinal region
7	Penis, scrotum	Excellent	Excellent	
8	Penis, scrotum	Excellent	Good	Skin graft on scrotum only 70% take; considerable scarring
9	Penis, scrotum	Excellent	Good	Testes still in upper thigh
10	Penis, scrotum	Excellent	Excellent	
11	Penis, scrotum	Good	Excellent	No skin graft; slight contracture penile skin
12	Penis, scrotum	Excellent	Excellent	
13	Penis, scrotum	Good	Excellent	No skin graft; slight contracture penile skin
14	Scrotum		Excellent	

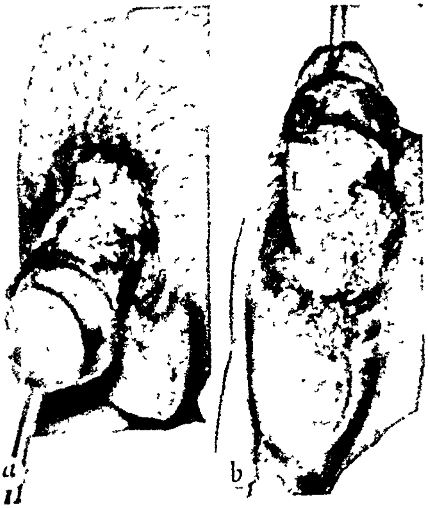

FIG. 1 (Case 5). Ninth day after application of split-thickness skin graft to shaft of penis and 15 days after temporary burial of left testis in left inguinal region. Note beginning lymphedema of cuff of foreskin. *a*, Dorsal surface; *b*, urethral surface.

Restoration of scrotum.—Here the problem is somewhat different. The manner in which small fragments of scrotum can be coaxed to grow into a full-sized scrotum in time is amazing, as Roth and Warren pointed out. For this reason, primary closure usually should be attempted. However, occasionally primary closure is out of the question because of infection. In these cases the testes are buried in the subcutaneous tissue of the inguinal region. This has seemed a better situation than the subcutaneous tissues of the upper part of the thigh because, with the testes in the inguinal region, less tension is exerted on the spermatic vessels and, consequently, the blood supply is less likely to be compromised.

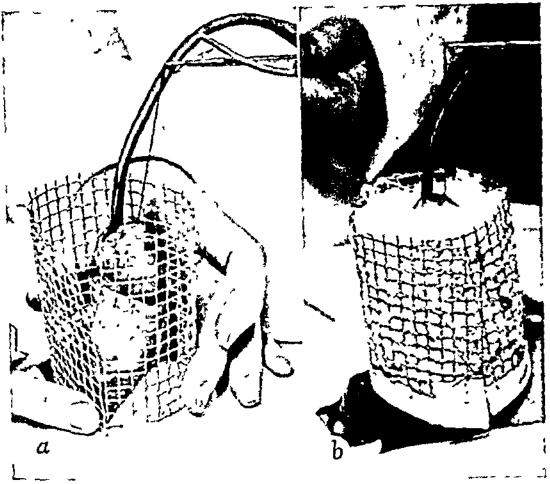

FIG. 2. Application of pressure dressing after skin grafting. *a*, Assistant holds penis erect by means of suture passed through glans, while surgeon makes trial application of wire fence. *b*. Enough teased, sterile, mechanic's cotton waste is placed around penis so that when fence is reapplied, waste will be compressed, finally fence is reapplied and fastened in place.

At a later date, when the infection has subsided but has not destroyed all viable fragments of scrotum, a Meyer-Torek or Cabot procedure can be carried out.

All viable scrotal tissue may be lost by avulsion or by sloughing consequent on infection. Fortunately, however, such complete loss is rare. When it does occur, the development of clean granulations to cover the testes is encouraged and, later, use of a split-thickness skin graft is recommended. Of course, the patient may elect to forego the skin grafting operation and to leave the testes in place in the tissue where they were surgically buried, as will be seen in a moment.

In cases 3, 7, 11, 12, 13 and 14 (table 1) primary closure of the scrotum was effected, in all cases with excellent results as far as the scrotum was concerned. It was necessary to bury one or both testes in the subcutaneous tissue in cases 4, 5, 6, 9 and 10, owing to infection in the scrotal region at the time of admission of the patients. Of these 5 cases, the testes were buried in the subcutaneous inguinal region in 4 and in the upper part of the thigh in 1. Three of the 5 patients elected to leave the testes so placed. In case 5 there was sufficient scrotum to form a sac for the right testis but it was necessary to bury the left testis in the inguinal region (fig. 1). The testis was brought down into a scrotal sac a year later by the Cabot technique. In case 10, both testes were first placed in the inguinal region; 3 months later the left testis was placed in a scrotal sac by a Meyer-Torek procedure and, several months after that, the right testis was brought into the scrotum by a Cabot procedure (fig. 3).

In cases 1, 2 and 8 (table 1) the infection was so marked that all remaining scrotal tissue sloughed away. When the patients were first examined, granulation tissue covered both testes. After moist antiseptic dressings had been applied for a few days, the granulation tissue was healthy and clean and a split-thickness skin graft was applied. The results were excellent, poor and good, respectively, in these three cases.

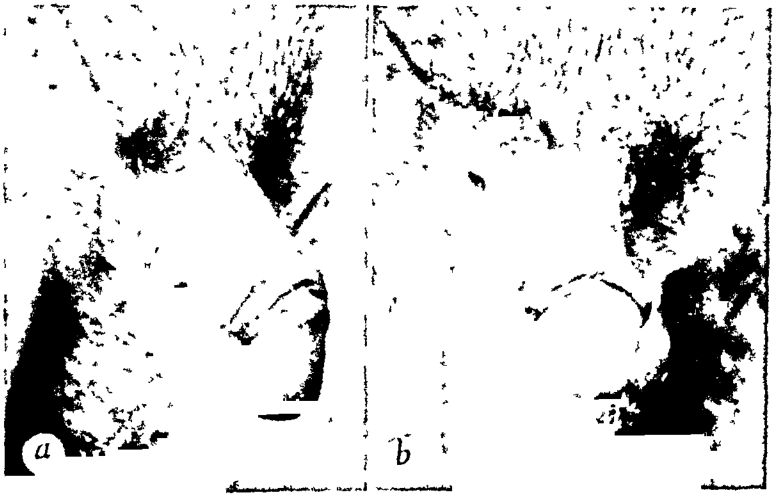

FIG. 3 (Case 10). *a* and *b*, Two views representing same case 1 year after accident. Grafted skin of penis is pliable and functions normally. Both testes are in a regenerated scrotum which is essentially normal.

SUMMARY

In the 11 cases of traumatic avulsion of the skin of the penis and scrotum reviewed herein, the skin of the penis usually was completely lost, whereas entire loss of the scrotum was unusual.

Covering of the denuded penis by means of a split-thickness skin graft gave excellent results. The grafted skin was flexible and moved easily on the shaft of the penis. If the site was not infected, the graft preferably was applied when the patient first was encountered, regardless of elapsed time since the accident. When obvious infection existed, it seemed wiser to promote healthy granulation first and to do a skin graft secondarily.

In restoration of the scrotum, to ignore the small fragments of scrotal tissue that nearly always remained would have been a serious mistake. Their regenerative power was amazing and they offered the only means of constructing a contractile, flexible sac to house the testes in normal position and at their normal temperature.

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CLINICAL ASPECTS OF INTERSEXUALITY[1]

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The natural occurence of a human intersex provides the practicing physician with an unenviable enigma. He must cope with a sexual morphological aberration, the genesis of which is prenatal and the ultimate somatic and sociological effects of which are postnatal. The later this stage of affairs is recognized, the more profound are the effects on those concerned, with the result that clinical management becomes more arduous and harassing. Indeed, determination of the true sex may prove an almost insurmountable problem. The predicament is further complicated by failure of experimental work to explain adequately the exact mechanism of sex differentiation.

Following Lillie's (1917) stimulating observation regarding the hormonal influences in the freemartin of cattle, there has been much investigative effort to duplicate naturally occurring intersexual phenomena in laboratory animals. A notable number of successes and paradoxes has resulted.

The primary chromosomal determination of sex is accepted. True hermaphroditism is recognized to be the result of genetic mutation. Pseudohermaphrodites are considered to be masculinized females (female pseudohermaphrodites) or feminized males (male pseudohermaphrodites). Beyond this point there seems to be little definitive agreement except that there is a difference in reaction depending on the species involved. This emphasizes the challenge for more diligent and unified application of the principles to human clinical investigation.

The respective proponents of the hormonal and genetic theories are in an active state of indeterminate dispute. The former have demonstrated the separate and combined effects of androgens and estrogens applied to the embryo or introduced into its environment. They have, furthermore, demonstrated the necessity for critical control of these influences with reference to intensity, timing, and duration. They are confounded by the paradoxical stimulation of mullerian derivatives by androgens and failure of estrogens to inhibit wolffian development under certain circumstances. More disturbing is the inevitable progress of sex differentiation in the absence of gonadal tissue. The natural embryonic maternal origin of these hormones has not been ascertained.

The genetic theorists have cited the hormonal paradoxes in favor of an inherited sex tissue sensitivity and direction. Lack of uniform correlation of gross physical appearance and histologic gonadal structure with the expressed libido and sex drives suggest a primary genetic sex tissue constitution. The reported familial occurrence in all grades of intersexuality is evidence of a hereditary tendency.

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[1] Read at annual meeting, South Central Section, American Urological Association, St. Louis, Mo., October 26, 1948.

Current progress in the field of experimental physiological genetics lends support to the merit of a combination of both theories Genetic modification of endocrine activity has been hypothesized and there is reported to be evidence of hormonal production of genic mutants The possibilities in connection with chemical and atomic modification in cancer research *may open an unlimited field for fruitful investigation* of intersexuality

Clinical observations and a cursory review of the literature reveal one rather interesting and fairly uniform phenomenon The persistence in the genetic female of the intense androgenic activity of the X-zone of the fetal adrenal cortex beyond its normal suppression at about the 20th gestational week results in development of male type external genitalia in an individual with internal female organs—a female pseudohermaphrodite Frequently, there is an immediate postnatal expression of adrenal cortical hypofunction which, if unrecognized and untreated, usually results in death

Recently two such cases came under observation through the facilities of our University Diagnostic Teaching Clinic and the Children's Hospital Interestingly, the patterns were almost identical. Both were infants 3 and 4 months of age One was admitted primarily because of a recurrent vomiting, diarrhea, and loss of weight, and the "hypospadias" was noted secondarily The other was admitted for recommendation regarding "hypospadias" complicated by urinary retention and recurrent fever, but because of a previously disregarded severe malnutrition and dehydration was placed under the primary care of the pediatric staff

No familial tendency could be elicited at this stage in either case The first patient was the third child in the family with a normal brother and sister The second was the only child of a 33 year old mother It was noted that the second mother had a positive serologic test for syphilis and antiluetic therapy had been started at about 6 months An interesting speculation is whether either of these events coincidental with the critical phase of embryonic development of the external genitalia may have been a factor in producing the abnormality in this mother's offspring

In both instances, a diagnosis of hypoadrenalism was made, and female pseudohermaphroditism was suggested as a strong probability The 17-ketosteroid values were normal

Following a period of treatment with regulated doses of adrenal cortical extract and supplemental sodium chloride, the general condition improved tremendously and urologic study was undertaken to verify or deny the possibility of female pseudohermaphrodism The findings are illustrated pictorially herewith.

The external genitals in both were male in type with hypospadias and bilateral "cryptorchism " In one, the urethral meatus was near the glans and an indeterminate mass, which was thought by some examiners to be a testis, but later proved to be cystic, was present in the right scrotal sac (fig 1) In the other, the urethral meatus was in the penoscrotal position (fig 2) Both had marked chordee The scrotum was well developed in each, although it was almost

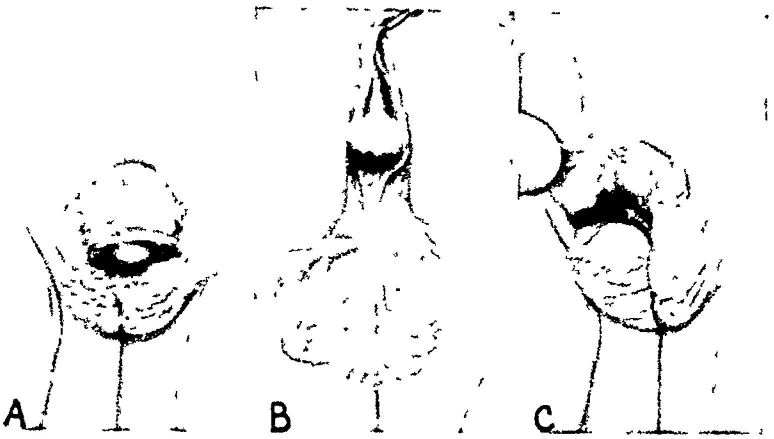

FIG. 1. Case of E. V. A, external genitalia. Phallus and scrotum well developed. No testes palpable. *B*, penoscrotal urethral meatus indicated by pointer. *C*, chordee and fusion of skin of scrotum to phallus is demonstrated.

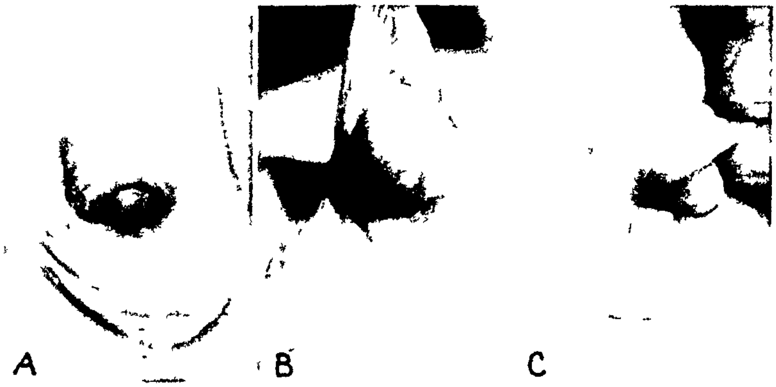

FIG. 2. Case of H. P. A, phallus and well developed scrotum in resting stage. No testes palpable. Small mass in right scrotal sac was a cyst. *B*, pointer is directed to a shallow pocket in penoscrotal position. Urethral meatus can be seen just beneath glans. *C*, chordee and fusion of skin of scrotum and phallus are demonstrated.

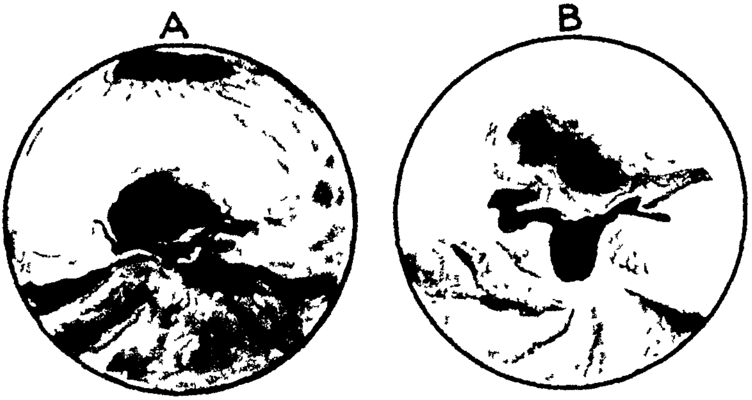

FIG. 3. Case of E. V. A, artist's sketch of [illegible] of "prostatic urethra." Bladder neck contour tends to feminine type. "Verumontanum" is atypical and utricle is exaggerated. *B*, close-up of "verumontanum."

identically fused to the skin covering the penis. "Dartos movements" were observed.

Urethrocystoscopy, using a miniature McCarthy cystoscope, revealed a normal bladder interior, a female type bladder neck contour, and atypical "prostatic urethra". The position of the external sphincter could not be identified. The "veru" was distinctly flattened and the orifice of the utricle was exaggerated (fig. 3). The marked structural similarity in these and other "hypospadias" cases has been striking although there is a difference in degree.

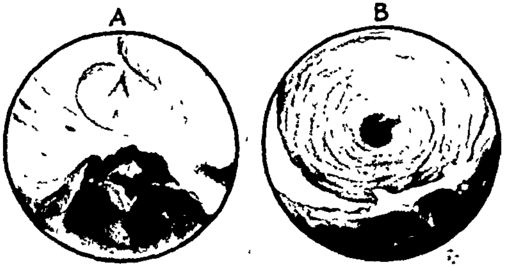

FIG. 4. Artist's sketch of atypical "prostatic" urethra in H. P. In *A*, veru is in foreground, irregular, flattened, and opening of utricle is very large. *In B, cystoscope has been introduced through utricle to visualize vaginal wall and os cervix.*

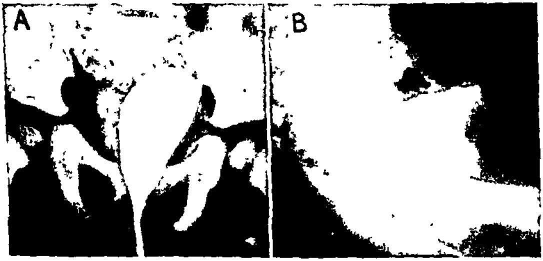

FIG. 5. Case of E. V. *A*, anteroposterior view of vagino-hystero-salpinogram obtained by injecting medium through catheter inserted into "utricle." *B*, lateral view of vagino-hystero-salpinogram. Bladder and urethra are also partially filled with medium.

In one, the cystoscope could be introduced through the orifice of the utricle and the interior of the sac, the walls of which were thrown into transverse folds, was visualized (fig. 4). A small opening thought to be a cervical os, was noted at the upper end of the "vagina". While the instrument was in place, Skiodan was injected and a vagino-utero-salpingo-peritoneogram was obtained (fig. 5).

In the other patient, the utricular orifice was so small that catheterization was required. After aspiration of about 15 cc of an unidentified milky material, which was not pus, Skiodan was injected and similar x-ray visualization was secured (fig. 6).

Recto-abdominal examination was performed in both under anesthesia. No prostate could be felt, but a small uterus, together with the adnexae and gonadal masses in ovarian position, was detected.

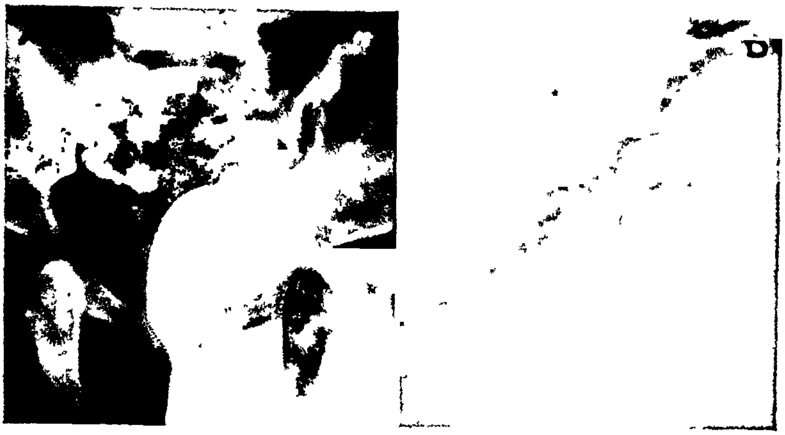

FIG. 6. Case of H. P. *A*, anteroposterior view of vagino-hystero-salpinogram secured by injecting medium through cystoscopic sheath positioned in opening at site of verumontanum. *B*, lateral view of vagino-hystero-salpinogram.

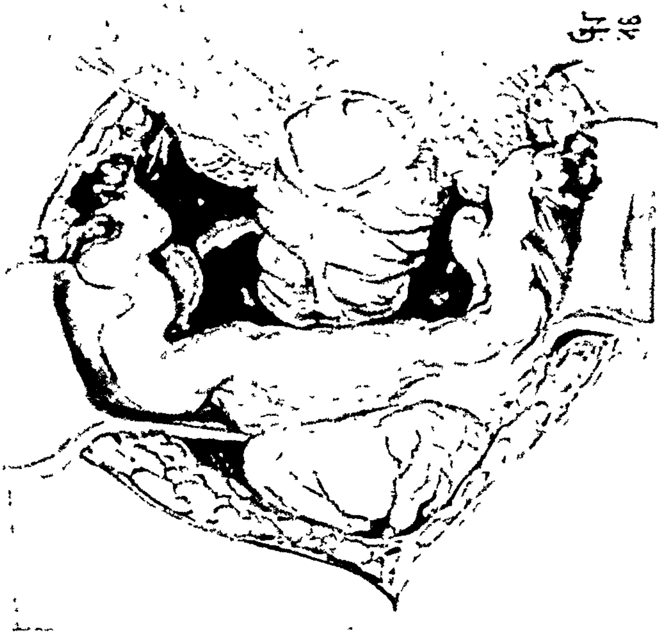

FIG. 7. Artist's sketch of findings by exploratory laparotomy. Small uterus with well developed tubes and typical ovaries are disclosed. No persistent wolffian elements were found.

Exploratory laparotomy in each revealed a small uterus with normally developed tubes and ovaries in proper position (fig. 7). No persistent wolffian elements could be found. The adrenals presented no palpable abnormality. Sections of each ovary were removed for histologic study and typical ovarian structure was reported.

Since the adrenal dysfunction was corrected by the pediatric staff and the genetic sex was definitely established as female in each instance, Hubert and Ernesto were returned to their parents' care to be reared as Hubertha and Ernestine. Subsequent observation and management is planned on an out-patient basis. Construction of a vagina should not be a major problem if and when a suitable age is reached. The reproductive function is not a factor since most of these persons are sterile, but their secondary sex drives are ordinarily manifest.

Following our adoption of a more critical attitude toward all hypospadias cases, we have observed at least two other intersexuals of major importance. One of these we know to be a true hermaphrodite with an ovary on the left side and testicle on the right side. The other is either a true hermaphrodite with ovotestes or a male pseudohermaphrodite. Since they have not been completely studied at this time, they will be reported in detail at a later date.

The clinical approach then resolves itself into the following general objectives. It is mandatory that a high index of suspicion be maintained toward all infants with genital abnormalities (notably hypospadias and bilateral cryptorchism) particularly if there is a family history of similar instances or if there is clinical adrenal cortical dysfunction. This is also true of postpubertal individuals who exhibit drives at variance with their assigned sex, or in whom there is alteration of normal physiologic sex processes.

The genetic and psychic sex must be recognized, if possible, at an early prepubertal phase. Among other procedures, gonadal biopsy is important. All *gonadal masses must be identified and their gross characteristics studiously appraised.* Sections for histologic study may be taken from several portions in an effort to avoid overlooking an ovotestis. Bipolar accummulation of testis and ovary in the same gonad has been reported. Longitudinal axial biopsy may be indicated in some. The results of ketosteroid and hormone assays have not proved significantly helpful in the prepubertal phase.

A conscientious effort must be made finally to achieve an acceptable anatomic, physiologic, psychic, and sociological adjustment for these innocently distorted individuals. Since there is as yet no pattern for attainment of this end, it still relies largely on the skill and ingenuity of the individual physician.

The foregoing remarks are illustrative of the magnitude and ramifications of the problems involved in human intersex, and emphasize the need for immediate unification of effort in meeting them. The multiplicity of manifestations which direct these individuals into almost all of the branches in the practice of medicine further supports this view. The incidence is probably much higher than is generally suspected.

The wisdom of establishing a Genito-Urinary Intersexuality Registry to collect and analyze data and to act in an advisory capacity should be seriously considered. Such an agency might function well in connection with some phase of the Child Welfare Program, Human Fertility, or Cancer Research. Correlated experimental and clinical data could thus be made generally available along with instructions and advisory progress bulletins as the need dictated. Such a project would provide invaluable aid to the investigator and clinician alike and solace to that segment of society consigned by fate to "the well of loneliness".

SUMMARY

Clinical and experimental relationships in dealing with intersexuality are discussed. Illustrative clinical cases are cited. A Genito-Urinary Intersexuality Registry for better correlation of data is suggested.

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THE PERMEABILITY OF COLLES' FASCIA FOR URINE

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It is a well known fact that in cases of rupture of the urethra the appearance of urine in the scrotum lags considerably behind its appearance in the superficial urogenital pouch. It is generally agreed that the order of extravasation is first the filling of the superficial urogenital pouch, then the scrotum and lastly the penis and abdomen.[1, 2, 3, 4, 5, 6, 7] According to the experiences of our urological colleagues, it may take 6 to 8 hours before the extravasated urine appears in the scrotum.

If, in conformity with the conventional descriptions of perineal anatomy, there were an open communication between the superficial urogenital pouch and the scrotal cavity, the delay in the filling of the scrotum would be difficult to understand. In a previous publication,[8] however, it was shown that in reality the "major leaf of Colles' fascia" extends uninterruptedly from the dorsal margin of the urogenital diaphragm forward across the top of the scrotal cavity, forming thus a fascial partition of considerable thickness between the superficial urogenital pouch and the cavity of the scrotum.

The object of the experiments reported in this article was to ascertain whether this fascial partition represents a temporary barrier to the passage of urine.

MATERIALS AND METHODS

The material used in these experiments was taken from 16 fresh cadavers.* The fasciae were removed on the day the cadaver was received except in 1 case when removal was deferred until the next day. To remove the fascia the skin was incised along the ischiopubic rami and these incisions were connected by a transverse incision ventral to the anus. The skin including the scrotum and testicles were reflected ventrally and discarded. The most cranial part of the scrotal septum was left behind. This operation exposes the leaf of Colles' fascia (our "major leaf") which lies between the superficial urogenital pouch and the scrotum. An incision was made through the fascia over the left ischiocavernosus muscle, the cut edge picked up and the fascia reflected to the right ischiocaverno-

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* Four additional runs have been made which are not recorded on the graphs. The results of these four runs parallel the majority as reported here.

sus muscle and then freed by a similar incision. The fascia was then immediately transferred to a vessel containing mammalian Ringer's solution and remained submerged in this solution until the test was run. After this leaf of Colles' fascia had been removed further dissection was made in eight cadavers to demonstrate the intact Buck's fascia and the tunica albuginea.[3]

The apparatus used for testing the permeability of the fascia to urine is shown in figure 1. It consists of a 5 gallon bottle supplied with a two-holed rubber stopper. It was connected to a source of compressed air via one hole of the stopper, and one limb of a "T" tube was inserted into the other hole. The other limbs of the "T" were connected with a mercury manometer calibrated in millimeters and with the testing tube. The testing tubes consisted of glass tubes approximately 100 mm long, 14 mm inside diameter, with a 1–1.5 mm flange on the lower end. These tubes accommodated about 15 cc of urine, and exposed an area of 154 mm.^{2} of the fascia to the urine (approximately $\frac{1}{18}$ of total area of the entire leaf of fascia). The fascia was placed over the lower end of the tube and secured above the flange with many turns of thread.

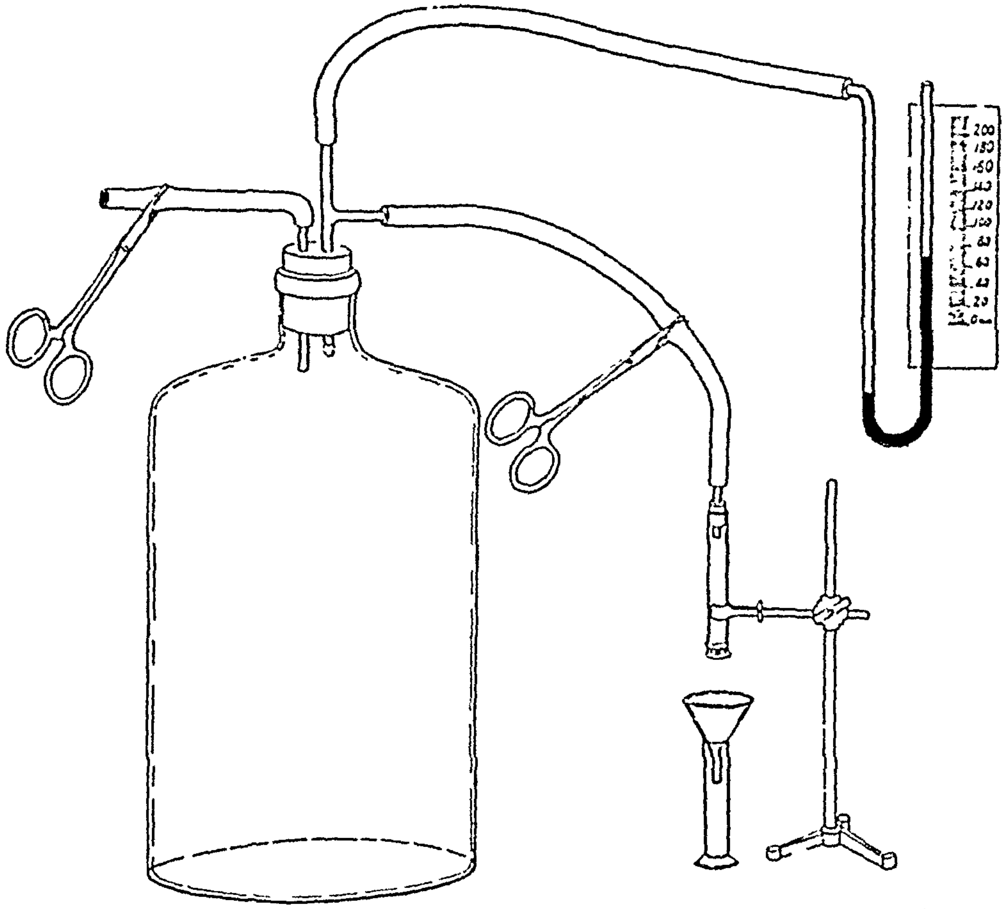

FIG. 1. Showing apparatus used to testing permeability of Colles' fascia. Detailed description in text

The procedure for testing a sample of fascia was as follows. The testing tube with the fascia attached was supported in a burette clamp and beneath it was placed a 25 cc graduated cylinder supporting a funnel. A 10 cc sample of fresh urine was poured into the tube and the tube was connected with the reservoir containing air under 70 mm. Hg pressure. Finally the clamp on the rubber tube from the reservoir was removed thereby putting the urine under 70 mm. pressure. There was no apparent change in pressure when the testing tube line was opened and the pressure was not allowed to vary during a test. The amount of urine that passed through the fascia was read at various intervals directly from the graduate cylinder to the nearest 0.5 cc. The time was recorded with a stop watch which was started as soon as the urine was subjected to pressure.

In some cases several tests were run on the sample of fascia. After most of the urine of the first run had passed through the fascia the connection with the pressure reservoir was clamped off. The testing tube was emptied of any residual urine, a fresh 10 cc sample was added, and a dry graduated cylinder was placed beneath the fascia. The testing tube was then reconnected with the reservoir and readings on the rate of passage were again made.

OBSERVATIONS

The permeability of the fascia from the various cadavers showed considerable variation. As seen in figure 2, when the total time of exposure is plotted against the amount of urine passed through the fascia there appear to be two definite groups of responses. The larger group shows curves of rather steep initial slopes followed in most cases by a gradual leveling off. This is the most common type of reaction and occurs in 14 of the 16 cadavers. In these cases there is a leveling off of the curve in the early minutes of exposure and in no case does the rate of passage increase with time, even in the three cases that were run longer than 150 minutes. The second smaller group consists of two experiments, Nos. 6 and 16, and presents an entirely different pattern. In both of these experiments the rate of passage was extremely high and remained so in spite of repeated passage of samples of urine.

If we consider only the first 10 minutes of each experiment we find these two groups even more clearly defined (fig. 3). Experiments 6 and 16 show a very steep slope throughout. The other experiments however show a very definite pattern. The initial slope is very much lower than in the first group, indicating a much slower passage and in four of the cases already shows a decrease during this period. When expressed in terms of the total area of the entire fascial leaf, it is seen that less than 64 cc of urine was passed through any of the fascial specimens in the first 10 minutes and in 8 of these cases less than 18 cc would have filtered through in 10 minutes.

In many of the experiments double runs were made, i.e. after most of the first sample of urine had filtered through the experiment was stopped and new samples of urine were added and the experiment performed again. The results of such a procedure were of two types as seen in figure 4. The upper graph representing one type and comprising 5 cases includes the two runs of 486-20. It will be noted that the first run shows a high initial rate of passage but that within a few minutes it begins to decline. At the end of 20 minutes the rate has declined to about 1

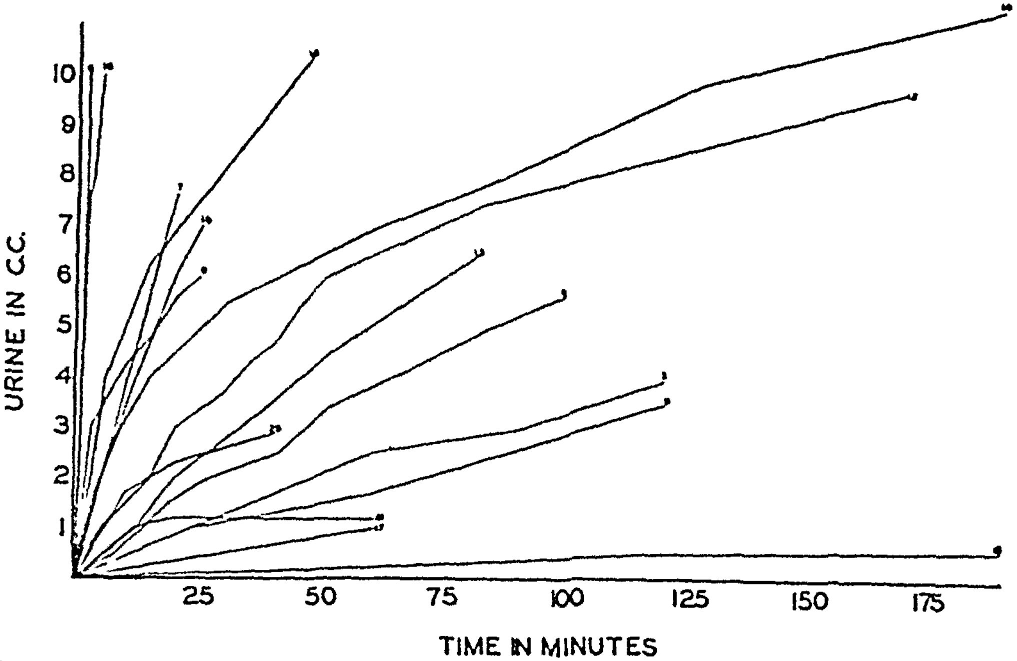

FIG. 2. Illustrates rate at which urine passed through the fascia of Colles' of 16 different cadavers, when exposed to a pressure of 70 mm. Hg. Small numbers indicate experiment numbers. Ten curves (Nos. 6, 7, 9, 10, 12, 14, 15, 16, 18, 20) represent averages of two runs, the other six (Nos. 3, 8, 11, 13, 17, 19) are results of single runs. Note an almost universal tendency towards decrease in rate of permeability as time of exposure increases.

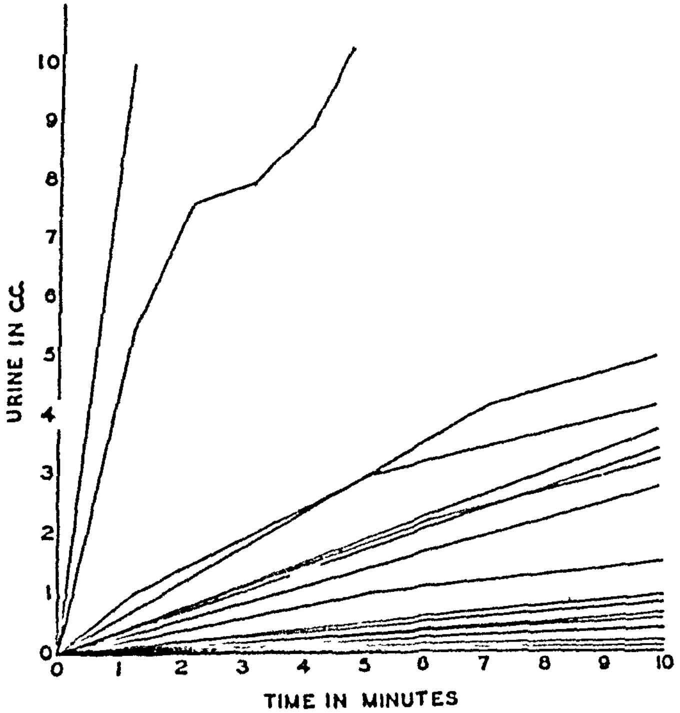

FIG. 3. Showing rate of passage of urine during first 10 minutes in all experiments charted n figure 2. Note separation of experiments into two groups.

cc in 40 minutes. In the second run the initial slope is not so steep as it was in the first run and at the end of 15 minutes a further decrease in rate is seen. The second type of result (represented by 5 cases) is exemplified by that seen in experiment 486-15; in this case there was no appreciable difference in rate between the two runs.

When the averages of the slopes of all the runs were taken together, a definite decrease in rate of passage is seen in relation to the time of exposure to the urine. In figure 5, the ordinate indicates the amount of urine in cubic centimeters, and the abscissa is a time interval of 10 minutes. The upper curve shows the average slope of 15 cases during the first 10 minutes of each case. The next curve shows the average slope of 13 cases during the second 10 minutes. The variation in the number of cases included in the averages is due to the fact that some of the experiments were run for longer periods of time than were others. These comparisons were not carried beyond 60 minutes as only 6 experiments were carried beyond this time. It will be clearly seen that the average slope is steepest during *the first 10 minutes and that there is considerable decrease in the rate of flow* between this and the 10–20 minute curve. There is a similar but not as great a decrease in rate between 20 and 30 minutes, and a still smaller decrease between 30–40 minutes. The rate of the 40–50 minute group being higher than the 30–40 minute group is possibly due to the fact that experiments Nos. 11 and 12 show a

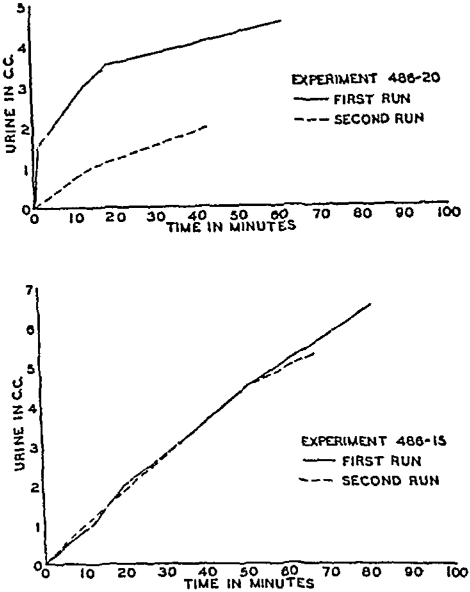

FIG. 4. Curves obtained by repeating test in same specimen of Colles' fascia. Experiment 486-20 gives two widely separated curves, while in 586-15 the two curves are almost identical.

steeper slope in that time range than they do before or after it. If the curves of these two experiments were smoothed, the 40–50 average would perhaps appear in the proper order. It will be noted that the 50–60 average is the lowest of them all and the general proposition that the rate of flow decreases with time of exposure is apparent.

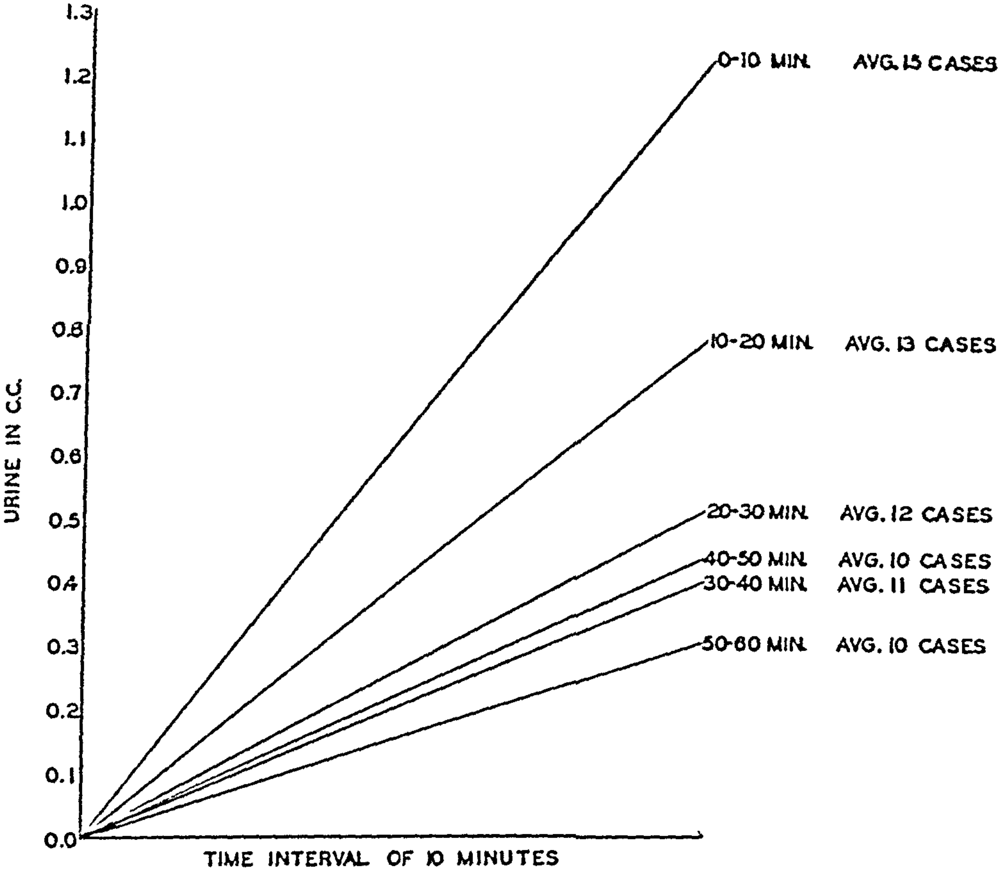

FIG. 5. Showing progressive decrease in rate of passage of urine through fascia with increasing time.

DISCUSSION

The experiments reported on the previous pages show that the permeability of Colles' fascia for urine is, in the majority of cases, so low that very little urine could pass through it even after relatively long periods of time. Apparently it is this property of Colles' fascia which accounts for the delayed passage of urine from the superficial urogenital pouch into the scrotum.

The objection may be raised that our experiments were performed on dead material, the physical properties of which may be quite different from those which Colles' fascia may show in life. So far no opportunity has offered itself to investigate this point. It is, however, well known that, in general, living tissues are less permeable than dead ones. Should this rule apply to the case in question, it would strengthen rather than weaken the force of the argument.

As mentioned above, the permeability tests were run with the urine under a pressure of 70 mm. Hg. This value was chosen arbitrarily, as we have no means of knowing the pressure under which the urine would be by the time it reaches the fascial partition. In cases of rupture of the urethra the intravesical pressure is probably considerably higher. But as the urine spreads through the space of the superficial urogenital pouch and through the tissues contained in it, much of the pressure under which it existed in the bladder must have disappeared by the time it is ready to permeate through Colles' fascia.

Before the series of experiments reported here was started, a number of preliminary experiments were performed in which the urine was not put under any pressure at all. Under these conditions, however, it was quite impossible to get any appreciable amount of urine through the fascia. Only a few drops would pass through the fascial specimens during the first 5 minutes; several specimens were exposed for hours without measurable quantities of urine accumulating in the collecting cylinder. It appears that this leaf of fascia is practically impermeable to urine unless the urine is placed under high pressure.

Although the fasciae tested here showed a wide range of permeability, the majority permitted only slow passage of urine. Anatomically we have observed that Colles' fascia is a laminated structure varying considerably in the number and thickness of the lamellae. In some cases the leaf is quite thick while in others is rather thin. These observed structural variations may account for some of the differences in permeability. It has also been observed in embalmed material that occasionally this leaf is perforated by small slit-like holes. It is possible that specimens Nos. 6 and 16 contained such holes and hence gave the appearance of being easily permeable.

The effect on the fascia of continued exposure to urine is of interest although we cannot tell at present to what degree it applies to the living fascia. The marked change in the slope of the curves indicates that the fascia becomes less permeable after a period of contact with the urine. In all experiments the fasciae were immersed in Ringer's solution until tested, hence the effect cannot be attributed to dehydration and rehydration of the fascia. In 7 cases (experiments Nos. 11, 13, 14, 15, 16, 17, 18) the fascia was allowed to remain in Ringer's solution for 1 to 2 hours at room temperature before the tests were run. The results of these particular experiments covered such a wide range (fig. 1) that this treatment was considered to have no effect. It is more likely that this change in permeability is due to a swelling action of the urine on the fascia. After the fasciae had been exposed to the urine for some time they appeared to have become much thicker, and it is possible that the decrease in permeability observed may be attributed to the swelling of the fibers with a resultant closing of the pores.

CONCLUSION

It appears that the major leaf of Colles' fascia which extends between the superficial urogenital pouch and the cavity of the scrotum is relatively impermeable to urine. In the majority of cases the fasciae reacted to the test in such a manner that they could be conceived as acting as a barrier in preventing the extravasated urine from immediately appearing in the scrotum. In general the permeability of the fascia became less after being exposed to urine for some time, and in no case was the permeability increased by the action of the urine.

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A RE-INVESTIGATION OF COLLES' AND BUCK'S FASCIAE IN THE MALE[1]

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Although the description of the membranous layer of the superficial fascia of the perineum and of the deep fascia of the penis is of venerable antiquity, both of them having been described first by Abraham Colles in 1811 and the latter one having been restudied by Buck in 1848, there remain even now several controversial points to be settled.

An appropriate idea as to how the anatomy of Colles' and Buck's fasciae is handled in our most popular anatomical texts may be obtained from an inspection of the account of this region contained in Gray's *Anatomy of the Human Body* (24th edition, 1942). Figure 1 is a reproduction of Gray's figure 402 (p. 418), a diagram picturing the course and relations of Colles' fascia. According to this diagram, Colles' fascia starts dorsally at the dorsal margin of the urogenital diaphragm, passes ventrally towards the root of the scrotum and is continued into the scrotal dartos. Its further course is not indicated in this diagram, but in the text on p. 422 it is stated that it is continuous with the "deep fascia of the penis" (i.e. with Buck's fascia) and with Scarpa's fascia. In Gray's figure 1119 (see our fig. 2) on p. 1247 of the same text, however, the relations between Colles' fascia and the penile fasciae is described in an entirely different way. Evidently under the influence of an article by Wesson, from which this illustration, modified in some details, was taken, Colles' fascia is shown there to be continued into the superficial (dartos) fascia of the penis, not into the deep fascia. There are three points of importance in the description of Colles' fascia as found in Gray's anatomy: 1) Colles' fascia does not pass across the top of the scrotal cavity and, consequently, the superficial urogenital pouch is in wide communication with the scrotal cavity; 2) the bulbocavernosus muscle lies deep to Buck's fascia; and 3) in the same text the relation between Colles' and Buck's fasciae receives a different description in two different parts of the book.

Similar to Gray's figure 1119 is Miley B. Wesson's figure 3 published in his 1927 article (The clinical importance of Buck's and Colles' fascia, Surg., Gynec. and Obst., 44: 208–213, 1927.) We reproduce Wesson's diagram in our figure 3; from it we learn that in Wesson's opinion Colles' fascia does not pass across the top of the scrotal cavity, leaving thus a communication between the superficial urogenital pouch and the scrotal cavity.

Whatever may be the actual relationships of Colles' fascia, the illustrations and accompanying texts leave usually no doubt, in which light their authors saw them. Quite different is the situation regarding Buck's fascia and its relation to the bulbocavernosus and ischiocavernosus muscles. Most of these illustrations and descriptions are restricted to Buck's fascia on the free portion of the shaft of the penis, while the relations of this fascia in the perineum, on the bulb of the urethra and on the crura, are either shrouded in haziness or are completely ignored. Among the many illustrations of the male perineum contained in the anatomical text by Testut-Latarjet (*Traite d'Anatomie humaine*, Paris, 1931, vol. v) for instance, there is not a single one which would clearly show the relationship between Buck's fascia and the penile muscles.

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[1] The investigations reported in this article were carried out with the support of several grants from the Weaver Fellowship Fund of the University of Maryland. The authors express their thanks to the trustees of the Fund.

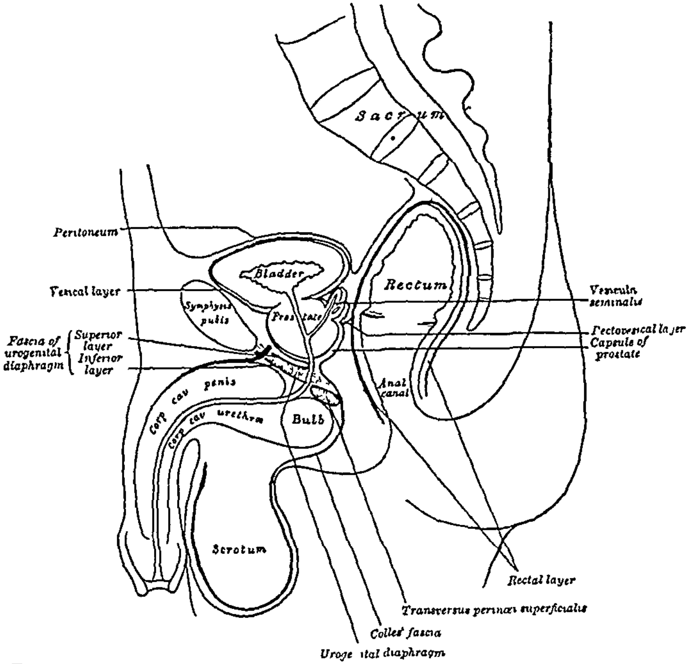

FIG. 1. Diagram from Gray's *Anatomy of the Human Body* 24th ed., 1942, figure 402 on p. 418. Colles' fascia is continuous with the scrotal dartos but leaves the scrotal cavity open against the superficial urogenital pouch.

In the anatomical atlas of Spalteholz (Werner Spalteholz, *Handatlas der Anatomie des Menschen*, 1st ed., 1903) there are two illustrations pertaining to this subject. From figure 657 on p. 592 (our fig. 4) one might be lead to believe that Buck's fascia encloses both the bulb of the urethra and the bulbocavernosus muscle, whereas in figure 674, p. 610 (our fig. 5) the muscles seem to be attached to the outer surface of Buck's fascia.

In Wesson's diagram referred to above (fig. 3) the bulbocavernosus muscle is not named, but a clear space is left between the bulb and Buck's fascia. If

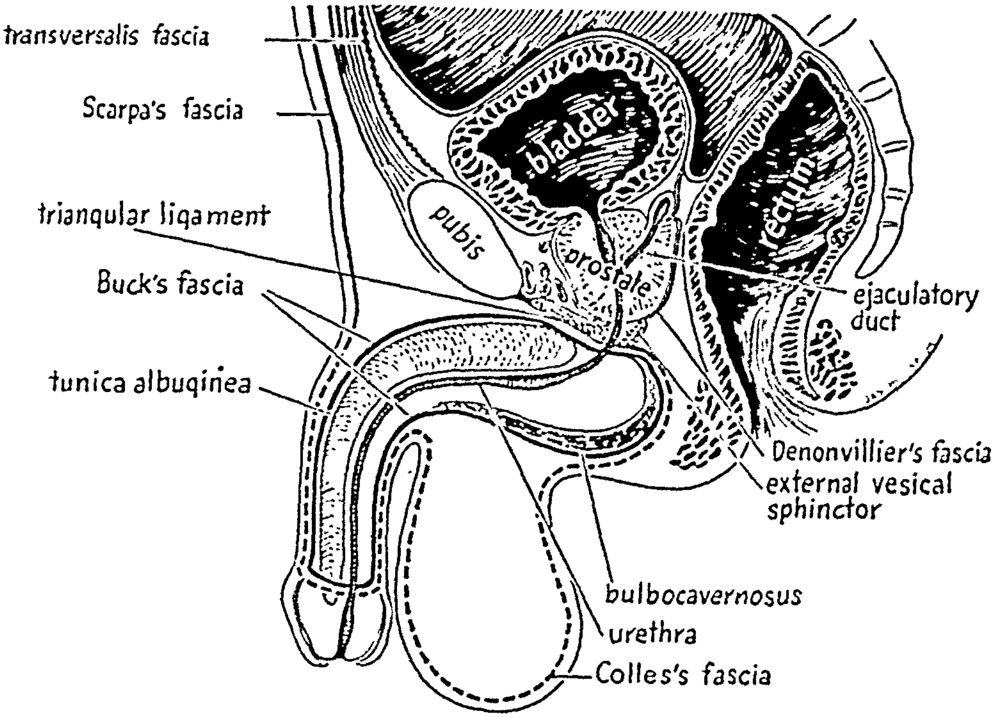

FIG. 2. Diagram from Gray's *Anatomy of the Human Body*, 24th ed., 1942, figure 1119 on p. 1247. Colles' fascia is continuous with both the scrotal and penile dartos, but leaves the scrotal cavity open against the superficial urogenital pouch. The bulbocavernosus muscle lies deep to Buck's fascia.

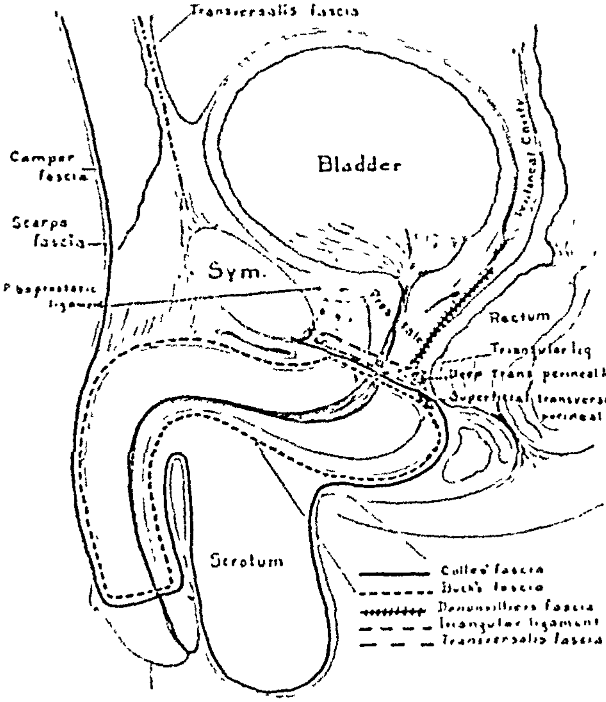

FIG. 3. Diagram from Wesson's article in Surg., Gynec. and Obst., 44: 208–213, 1927. Colles' fascia does not extend over top of scrotal cavity, leaving latter open against superficial urogenital pouch. Bulbocavernosus muscle lies deep to Buck's fascia.

this is supposed to indicate the location of the muscle, the author believed evidently that the bulbocavernosus lies deep to Buck's fascia. This relationship between fascia and muscle is the one quite clearly illustrated in Gray's diagram mentioned previously and shown in our figure 2.

Most recently Tobin and Benjamin (Anatomical Study and Clinical Consideration of the Fasciae Limiting Urinary Extravasation from the Penile Urethra, Surg., Gynec., and Obst., **79**, 195–204, 1944) devoted a special investigation to this topic. In their opinion the relations of Buck's fascia as illustrated by Wesson and Gray, would be correct. They not only present a perfectly clear illustration in their figure 11, reproduced in our figure 6, according to which both the bulbocavernosus and ischiocavernosus are located deep to Buck's fascia, but they state specifically on p. 198 of their article: "The bulbocavernosus and ischiocavernosus muscles are internal to Buck's fascia."

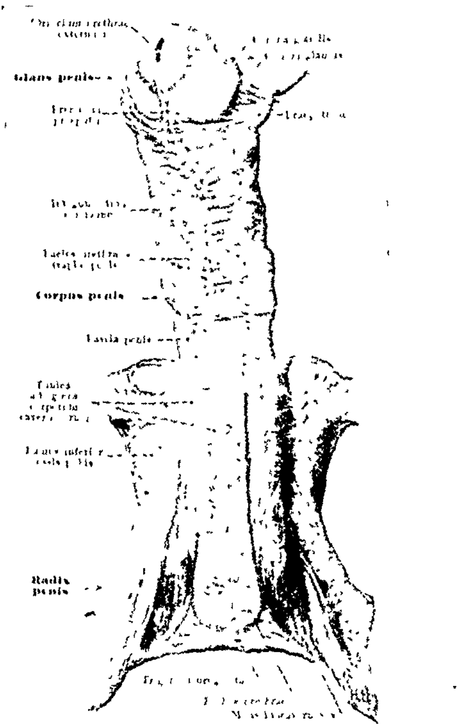

FIG. 4. Reproduction of figure 657, p. 592 of Spalteholz' *Handatlas der Anatomie des Menschen*, 1st edition, 1903. Buck's fascia seems to lie superficial to bulbocavernosus and ischiocavernosus muscles.

I. OUR THESIS

We have made many dissections of the male perineum, both together with the medical students and in our own research laboratories, using embalmed as well as fresh cadavers; but in every instance our observations have been very different from those reported by other investigators. No matter how variable the perineal fasciae may be in other respects, in four points there has been perfect agreement between all our dissections: 1) the major leaf of Colles' fascia forms an easily demonstrable partition across the top of the scrotal cavity; 2) consequently there is no direct anatomical communication between the superficial

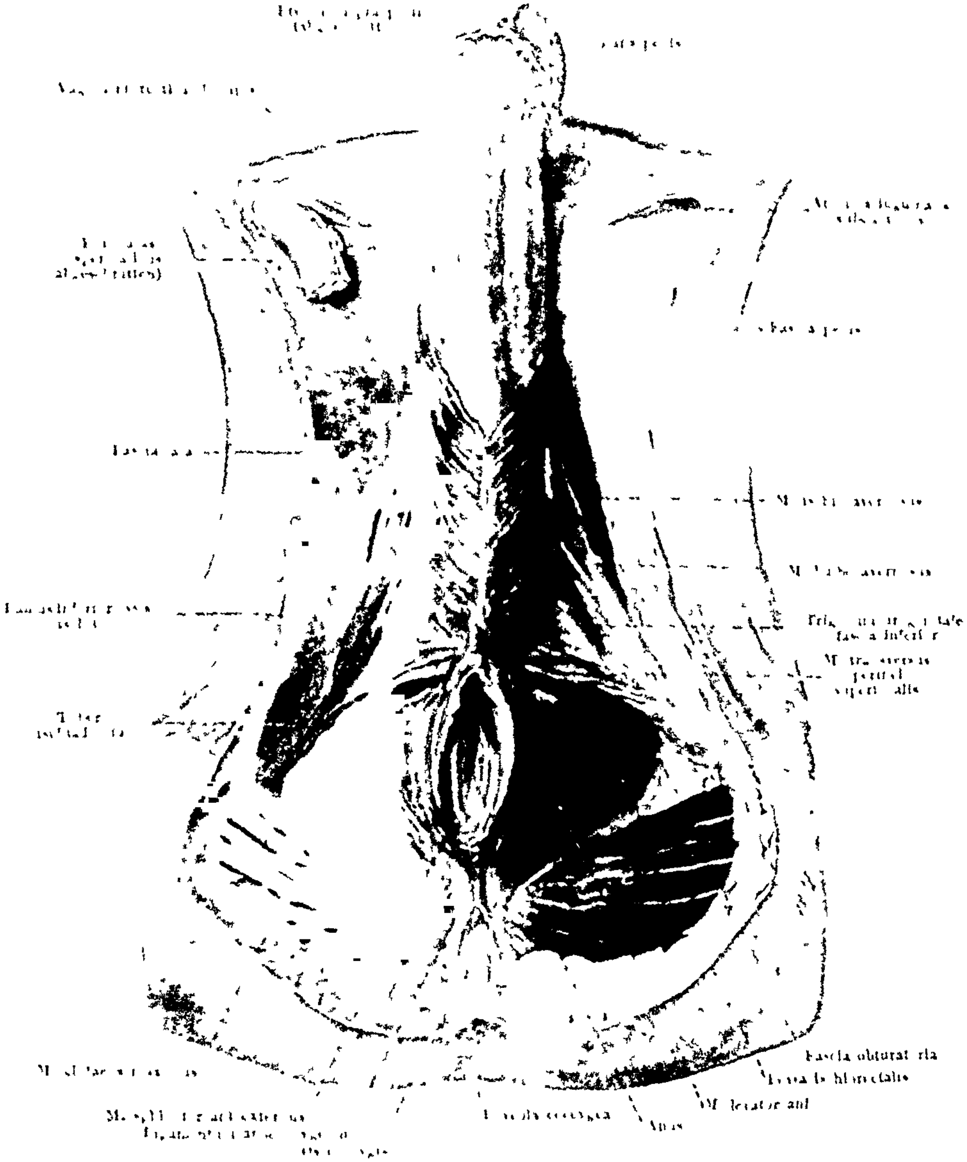

FIG. 5. Reproduction of figure 671 on p. 610 of Spalteholz, Handatlas. Buck's fascia seems to lie deep to the penile muscles.

urogenital pouch and *the scrotal cavity, except in those cases in which the major* eaf of Colles' fascia is perforated by transverse slits; 3) both the bulbocavernosus and ischiocavernosus muscles lie distinctly superficial to Buck's fascia; they are separated by Buck's fascia from the albuginea, and 4) Colles' fascia is by no means continuous with the deep "fascia penis"; its continuation on the penis is represented by the superficial fascia (dartos) of the penis.

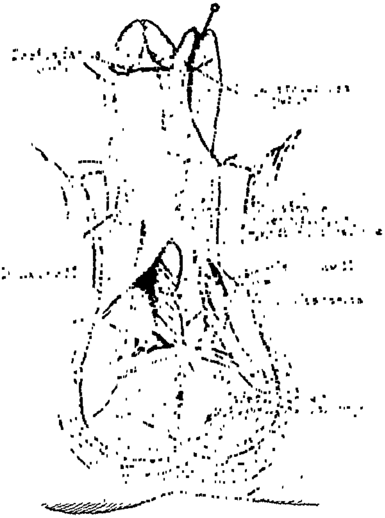

FIG. 6. Reproduction of figure 11 of the article by Tobin and Benjamin in Surg., Gynec. and Obst., 79: 195–204, 1944. A fascia placed superficial to bulbocavernosus and ischiocavernosus muscles is claimed to be Buck's fascia.

II. DEMONSTRATION OF THE FOUR POINTS MENTIONED IN THE PREVIOUS PARAGRAPH

A clear and accurate dissection of the perineum is a laborious task; because of the many fascial layers, the variability in their number and the occasional fusion *of some of them, confusion and misinterpretation of the fasciae are apt* to occur. But after some experience has been acquired, it is easy to prepare simplified dissections which are free of the bewildering view of detailed dissections and yet are suitable to demonstrate the essential points. For these *reasons it seems convenient to discuss these points first with the aid of simplified* dissections.

One of these is illustrated in figure 7 (464_3, 1941, fig. 22) showing a photograph *of the dissection of the perineum of a Negro, aged 42 years. After removing the skin of the perineum, the two halves of the scrotum are reflected laterally*; but the scrotal septum is left in place. Colles' fascia is now seen as it extends forward in one continuous sheet; this part of Colles' fascia is the "major leaf" of Colles' fascia. Ventrally, as the illustration shows, it is continued directly into a cylindrical evagination which in this dissection has been rolled back upon itself; this is not Buck's fascia but the superficial fascia of the penis or penile dartos; Colles' fascia is continued into the superficial fascia of the penis. Buck's fascia is seen exposed upon the shaft of the penis; it has no connection with Colles' fascia. Lateral and ventral to the root of the free part of the penis the major leaf of Colles' fascia is found continuous with the abdominal fascia (not shown in illustration). The fascial layer of the scrotal wall, the scrotal dartos, as is well seen in the illustration, takes origin everywhere from the major leaf of Colles' fascia; and the scrotal septum is likewise attached to this layer of Colles' fascia. None of the manipulations performed so far have resulted in opening the superficial urogenital pouch; the penile muscles are not seen and neither the urethral bulb nor the crura have been exposed. The major leaf of Colles' fascia forms a floor for the superficial urogenital pouch, which, ana-

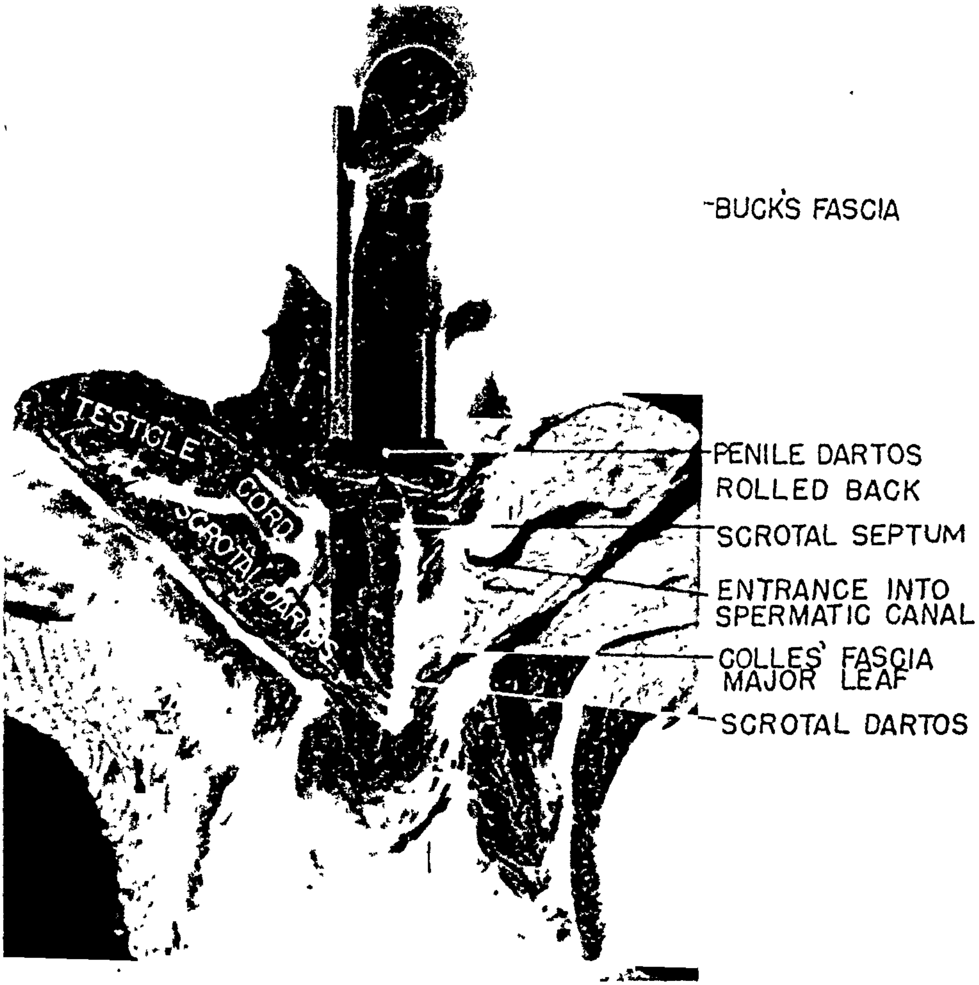
BUCK'S FASCIA
TESTICLE
CORD
SCROTAL DARTOS
PENILE DARTOS ROLLED BACK
SCROTAL SEPTUM
ENTRANCE INTO SPERMATIC CANAL
COLLES' FASCIA MAJOR LEAF
SCROTAL DARTOS

FIG. 7 Dissection of Negro male (461_3, 1911, fig. 22) aged 42 years. Colles' fascia stretches across top of scrotal cavity; it forms a partition between scrotal cavity and superficial urogenital pouch. On shaft of penis Colles' fascia is rolled back upon itself, exposing Buck's fascia. Walls and septum of scrotum arise from Colles' fascia.

tomically speaking, separates completely the cavity of this pouch from the scrotal cavity As Colles' fascia passes forward from its dorsal origin, it is split into the major leaf and into the scrotal dartos, the latter, therefore, may be said to represent an evaginated superficial leaf of Colles' fascia

In the ventrolateral corner of the scrotal sac is seen an opening into which the spermatic cord enters (fig 7) This opening can be demonstrated to be the entrance into a fascial canal which we are accustomed to call the "spermatic canal" since it serves the passage of the spermatic cord This canal ascends, lateral to the penis, into the abdomen and opens opposite the subcutaneous inguinal ring Owing to the presence of this canal the scrotal cavity communicates with the abdominal fascial pouch

It is well known that one of the distinctions between Buck's and Colles' fasciae is the manner in which they are attached to the layer immediately below them Whereas Buck's fascia is firmly adherent to the penile albuginea, Colles' fascia is only loosely attached to Buck's fascia For this latter reason it was possible, as shown in the illustration, to roll Colles' fascia back upon itself and for the same reason the major leaf of Colles' fascia is lifted away from the deeper structures if one pulls upon the septum of the scrotum

In the subject illustrated in figure 7 Colles' fascia formed a continuous membrane, devoid of any defects But there are cases in which this fascia is perforated by a row of transverse slits, as shown in figure 8 (464_2, 1941, fig 14) It is interesting to note that Hermann Braus, in figure 245 of vol 2 of his *Anatomie des Menschen* (2nd edition, 1934) illustrated what is evidently our major leaf of Colles' fascia perforated like the one shown in our figure 8 Incidentally, from Braus' illustration one is led to believe that he saw the relation of Colles' fascia as it is described here, forming a partition between scrotal cavity and superficial urogenital pouch But he makes no reference to this point in the text of his book

In order to ascertain accurately the relations between Buck's and Colles' fascia and especially the relation between Buck's fascia and the penile muscles, it is indispensable that the fascial layers be dissected, layer by layer, starting from the corona of the penis all the way back to the dorsal ends of the urethral bulb and the crura A simplified dissection of this kind, showing to better advantage the relations of Buck's fascia is shown in figure 9 (479_{43a}), it illustrates the perineum of a white man, aged 79 years, after the skin had been raised, the scrotum cut away and Colles' fascia reflected Colles' fascia is seen forming one continuous layer with the superficial fascia (dartos) of the penis The reflection of the major leaf resulted in the opening up of the superficial urogenital pouch and in the exposure of the muscles (The details of such a dissection will be discussed later) The perineal muscles of this subject were unusually large and thick and of deep red color and therefore especially suitable for this study By the reflection of Colles' fascia Buck's fascia has been exposed It is seen reflected from the right half of the urethra, beginning at the corona and extending dorsally to the end of the urethral bulb On the left side, at the place where the left crus joins the shaft of the penis, this fascia is seen to be continued from the corpus cavernosum penis upon the crus. On both the bulb and the crus Buck's fascia can be seen passing deep to the penile muscles (the bulbocavernosus and ischiocavernosus muscles). On the left side the muscles have been left undisturbed; on the right side the bulbocavernosus muscle has been dissected away from Buck's fascia. Those who claim that the bulbocavernosus muscle lies deep to Buck's fascia might argue that we are taking the albuginea for Buck's fascia. We are therefore obliged to stress several criteria which permit unfailingly the identification of Buck's fascia. If the layer pronounced above as Buck's fascia were the albuginea, the spongy tissue of the corpus cavernosum urethrae should have been exposed by the reflection of this layer. Instead, however, we find deep to this layer another layer which in the embalmed cadaver has a whitish color and somewhat leathery consistency; it is shown, in the illustration, incised in one place, and through the slit is seen the spongy tissue of the corpus cavernosum urethrae, which in the embalmed cadaver is

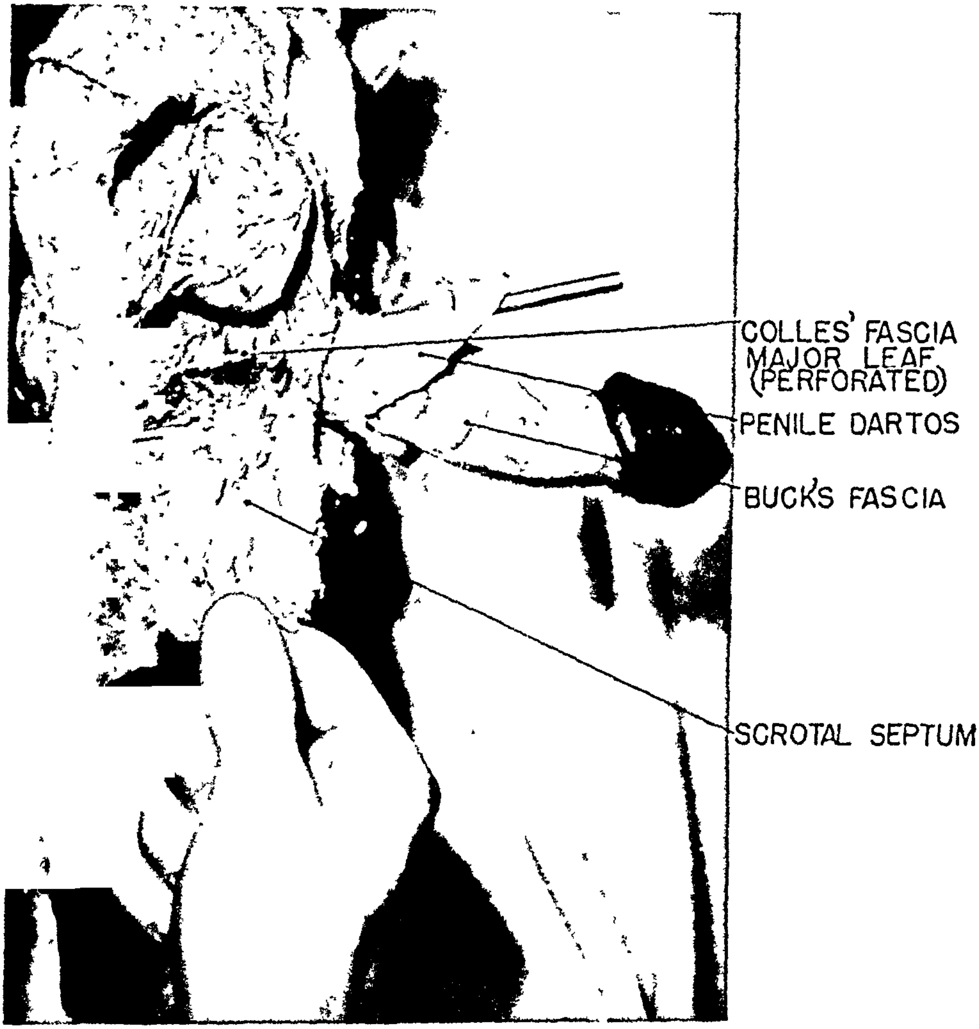

FIG. 8. Dissection of male perineum (161½, 1911, fig. 11). A case in which Colles' fascia is perforated by slitlike openings. Also notice attachment of scrotal septum to Colles' fascia.

brittle and granular and of red color, not unlike coagulated blood. This layer can be dissected away from the spongy tissue over the entire length of the urethra as was done in this case after the illustration had been made; it is obviously the albuginea. We have, therefore, demonstrated the three main layers generally

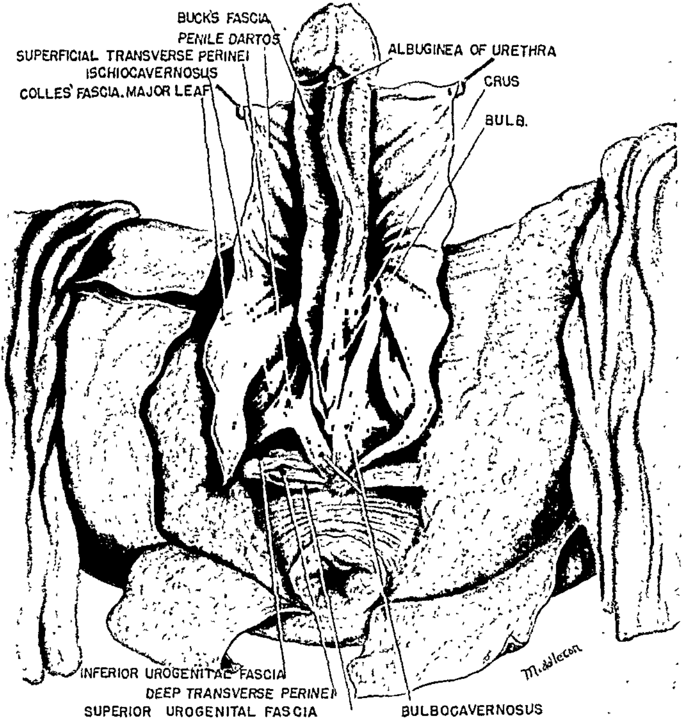

FIG. 9. Dissection of white male ($479_{43\,a}$, 1946, fig. 1), aged 79 years. Colles' fascia reflected from perineum and penis in one continuous layer. Buck's fascia reflected on right side, albuginea of urethra exposed and incised to show substance of corpus cavernosum urethrae. Notice that bulbocavernosus and ischiocavernosus muscles lie superficial to Buck's fascia.

described in the anatomical texts, the superficial fascia or fascia of Colles, the deep fascia penis or Buck's fascia and the albuginea. Of these three layers only one, Colles' fascia, lies superficial to the penile muscles, while the other two, Buck's fascia and the albuginea lie deep to these muscles. Another criterion of Buck's fascia is the fact that it forms a septum between the urethra and the corpus cavernosum penis; this septum has been displayed in the dissection illustrated in figure 9; it is seen at the place where the urethra was pulled over to the left side and is continuous with the leaf of Buck's fascia, which was reflected off the urethra. A third criterion of Buck's fascia is its texture. Colles' fascia is of a felt-like texture and feels soft, whereas Buck's fascia is dense and firm and aponeurotic in nature, quite similar in these respects to the inferior urogenital fascia. The aponeurotic nature of Buck's fascia has already been well described by Colles in 1811; on p. 146 he observes that the penis possesses a special fascia which is of the nature of a "ligamentous membrane" and is derived from the "suspensory ligament." Although Colles used the term of suspensory ligament for a structure described now as composed of two different ligaments, a superficial or fundiform and a deep or suspensory ligament, he differentiated nevertheless quite accurately between these two portions of his suspensory ligament. Of the deep portion which arises from the symphysis pubis and corresponds to our suspensory ligament, he states that it has a perfectly ligamentous texture and expands over the crura, over the urethra and over the penis itself terminating at the base of the glans and thus furnishing a complete and special envelop for the penis.

The dissection shown in figure 9 demonstrates that the bulbocavernosus and ischiocavernosus muscles lie superficial to Buck's fascia; they are separated from the albuginea by this fascia.

III. ELABORATE DISSECTION OF THE FASCIAE

The relations described so far were found to be constant in all our dissections. They were verified also in 10 dissections of fresh, unembalmed cadavers. In more elaborate dissections other structures are revealed which are more difficult to display and some of which are variable. These will be shown in successive steps of a dissection of a white male (479_{rth}, 1947) aged 48 years.

1) Tela subfascialis. In figure 10 (479_{rth}, 1947, fig. 2) one of the initial stages of the dissection is shown. The two halves of the scrotum, the right one together with the septum, have been reflected. The left half of the major leaf of Colles' fascia is seen as it forms the partition between scrotal cavity and superficial urogenital pouch. On the penis Colles' fascia (penile dartos) has been incised and reflected. Deep to it a second layer of superficial fascia was found, incised and likewise reflected. The superficial layer is joined by the dartos of the scrotum. The deep layer represents probably Eberth's (Die männlichen Geschlechtsorgane. In Bardeleben's *Handbuch der Anatomie,* Gustav Fischer, Jena 1904) "Tela subfascialis." In some subjects as many as 3 to 5 layers of Colles' fascia can be dissected and displayed as separate and individual membranes. In fresh cadavers and in the living subject the tela subfascialis is difficult to display as it is of loose texture and easily broken down by the operator's instrument or finger.

The fascia exposed on the shaft of the penis by the reflection of the two layers of Colles' fascia is the fascia of Buck as will be shown later on.

2) Deep septum of Colles' fascia and the fascial compartment of the bulbocavernosus muscle. Figure 11 (479_{rth}, 1947, fig. 4) shows one of the more advanced stages of the dissection Buck's fascia has been raised from the urethra, and on the corpus cavernosum penis it was incised and slightly reflected to the left The albuginea was exposed and incised *on the urethra* to display the spongy substance On the *corpus cavernosum penis* the albuginea is seen through the incision of Buck's fascia, but has been left undisturbed as yet The major leaf of Colles' fascia has been *split along the left side of the scrotal septum*, deep to Colles' fascia the bulbocavernosus muscle is visible Moreover it is seen that the major leaf of Colles' fascia gives off a septum, *called henceforth* the "deep *septum" which is seen passing deep to the bulbocavernosus muscle*

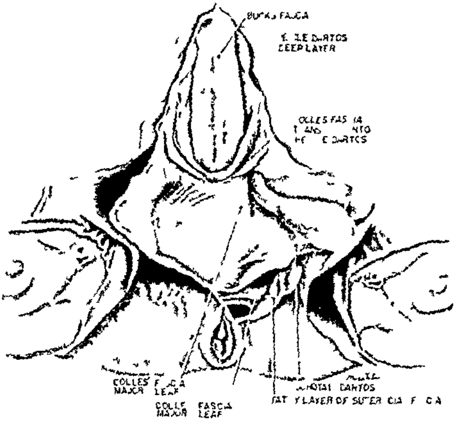

FIG 10 Perineal dissection of a white male (479_{43h}
major leaf of Colles' fascia forms the roof of the scrotal
with the penile dartos which together with a deeper laye
been reflected to expose Buck's fascia The parts of scrotal dartos arise from major leaf of Colles' fascia In left ventral corner of scrotal cavity lies entrance into left spermatic canal

In order to investigate further the relations of the deep septum the dissection was advanced to the stage shown in figure 12 (479_{43h}, 1947, fig 5 a) The major leaf was cut through transversely just dorsal to the place where the deep septum arises from it and *the flap so obtained* was reflected to the left Moreover the muscle and the deep septum were cut through along the midline all the way to the end of the bulb The bulbocavernosus muscle and its constrictor radicis penis portion are now fully exposed, the latter one sweeping laterally across the left crus, but the crus itself is not yet visible

From this dissection it is evident that the deep septum of *Colles'* fasciae remains distinct as an individual layer from its origin to the end of the bulb Hence the bulbocavernosus muscle is separated in its entire extent from the albuginea by Buck's fascia and a deep septum of Colles' fascia Not only does it lie superficial to Buck's fascia, but it is indeed further separated from it by a deep layer, the deep septum, of Colles' fascia. The major leaf of Colles' fascia and the deep septum together form a fascial compartment for the bulbocavernosus muscle.

3) Fusion of fasciae. In this dissection also the other, deeper layers were followed dorsally into the perineum. In order to display them, the left half of the bulbocavernosus and the corresponding part of the deep septum were thrown laterally to the left, as shown in figure 13 (179_{bh}, 1947, fig. 5 b). The

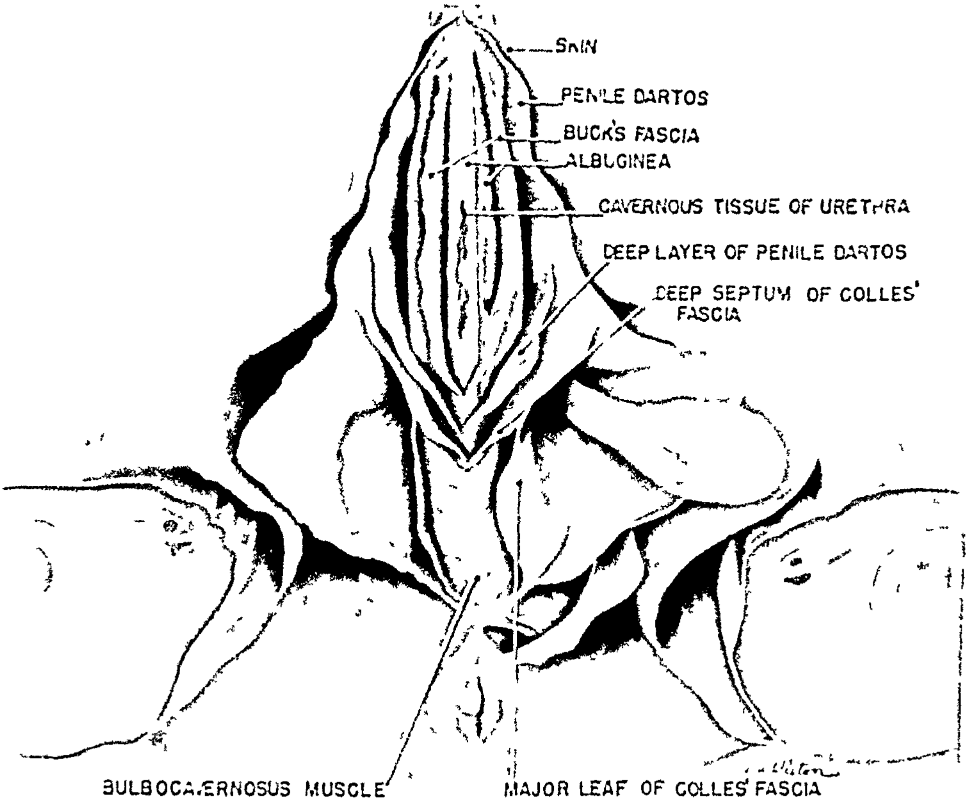
SKIN
PENILE DARTOS
BUCK'S FASCIA
ALBUGINEA
CAVERNOUS TISSUE OF URETHRA
DEEP LAYER OF PENILE DARTOS
DEEP SEPTUM OF COLLES' FASCIA
BULBOCAVERNOSUS MUSCLE
MAJOR LEAF OF COLLES' FASCIA

FIG. 11. Further advanced stage of dissection shown in figure 10 (179_{bh}, fig 4) On penis, Buck's fascia, both on urethra and on corpus cavernosum penis, has been reflected; albuginea has been exposed and, on urethra, has been incised to display spongy tissue of corpus cavernosum urethrae. In perineum, major leaf of Colles' fascia has been incised and retracted; bulbocavernosus muscle is exposed and a "deep septum" arising from Colles' fascia is seen as it passes deep to muscle

albuginea was dissected to the end of the bulb; the spongy substance of the urethral corpus cavernosum was thus exposed. Also Buck's fascia was dissected to the end of the bulb. Throughout the entire extent of the urethra it retains its individuality, a condition found in all our dissections, also in those of fresh cadavers. The deep layer of Colles' fascia, designated above as tela subfascialis, cannot be demonstrated as a separate layer in the perineum. At the place where the crus branches away from the penile shaft, this fascia fuses with Buck's fascia and fades away on it. Evidently it is of use only on the free part of the penis, where it serves to permit free movement of the skin and dartos over Buck's fascia

4) *The crural septum* A reinspection of figure 12 will be helpful in visualizing that reflection of the major leaf of Colles' fascia, while it exposes the bulbocavernosus muscle, does not bring into view the crus and its muscle The location of these structures, however, is indicated by a roundish ridge just lateral (to the left) of the bulbocavernosus muscle In order to display the crus, an incision must be made along the ridge This stage of the dissection is shown in figure 14 (479_{43h}, 1947, fig 6) Colles' fascia sends a septum into the space between the bulb and the crus which covers the crus and the ischiocavernosus muscle and fuses with the crus close to the inferior urogenital fascia

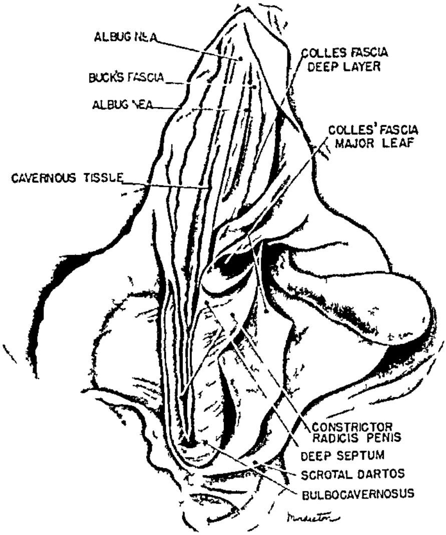

FIG 12 Same dissection as figures 10 and 11, still further advanced (479_{43h}, fig 5 a) Major leaf of Colles' fascia cut through transversely along constrictor radicis penis portion of bulbocavernosus muscle and reflected, on left side Bulbocavernosus muscle incised to show that deep septum of Colles' fascia extends all the way dorsal to end of bulb Bulbocavernosus muscle lies superficial to both deep septum and Buck's fascia To left of perineal urethra a roundish ridge is visible, in it are hidden left crus and ischiocavernosus muscle, both of them covered by a fascial septum (the crural septum) which arises from major leaf of Colles' fascia (see fig 14)

5) *The fasciae on the crura* We have seen that on the perineal portion of the urethra four layers remain distinct all the way to the end of the bulb These are the major leaf of Colles' fascia, the deep septum of Colles' fascia, Buck's fascia and the albuginea On the crura only two layers retain their individuality all the way to the tip of the crus The first layer which fades away on Buck's

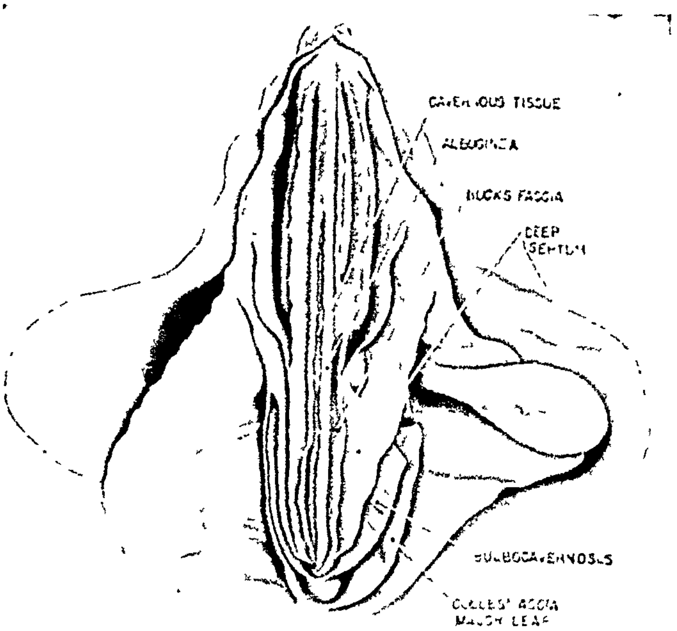

FIG. 13. Dissection shown in figures 10, 11 and 12 ($179_{B\,b}$, fig. 5 b), after left bulbocavernosus muscle and left half of the deep septum had been reflected laterally, to left. Buck's fascia was exposed, incised to dorsal end of bulb and reflected to display albuginea on urethra. Then incision through albuginea, started on the urethra of the shaft (see fig. 11) was prolonged dorsally to end of bulb in order to expose spongy tissue along full length of urethra. On urethra both Buck's fascia and albuginea retain their individuality throughout course of urethra.

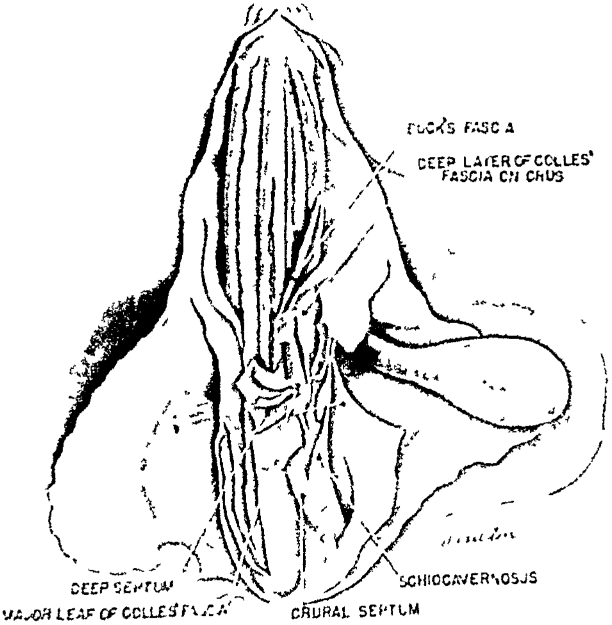
BUCKS FASCIA
DEEP LAYER OF COLLES' FASCIA ON CRUS
DEEP SEPTUM
SCHIOCAVERNOSUS
MAJOR LEAF OF COLLES' FASCIA
CRURAL SEPTUM

FIG. 14. Same dissection as figures 10–13, continued ($179_{B\,b}$, fig. 6). The crural septum over the roundish ridge seen in figure 12 has been incised, left crus and ischiocavernosus muscle are exposed. Gradual fusion of fascial layers over crus is visible, but both albuginea and Buck's fascia remain deep to ischiocavernosus muscle.

fascia is the tela subfascialis, as has been mentioned above. In figure 14 the place where the left crus separates from the urethra is seen, located about $\frac{3}{4}$ of an inch above the constrictor radicis penis; at this place it begins to be difficult to separate the deep layer of Colles' fascia from Buck's fascia and finally this deep layer *fades away completely*. At the place where the deep septum arises from Colles' fascia, this septum is still quite distinct as an individual layer on the crus. It can be *followed dorsally as far as the constrictor radicis penis bundle*; at this point it fuses with the tendon of this bundle and *finally*, still further dorsally, *fades away upon the fascia of Buck. And Buck's fascia itself, in the region of* the ischiocavernosus muscle, loses its identity, as it fuses intimately with the albuginea. Therefore, in this subject, as shown in figure 15 (479_{13b}, 1947, fig. 7)

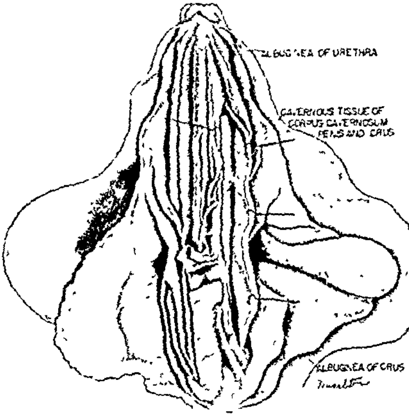

FIG. 15. Last stage of dissection shown in figures 10–14, (479_{13b}, fig. 7). Albuginea together with other layers fused with it, is incised over the left crus and reflected.

there are only two layers present at the dorsal end of the crus. One layer which lies deep to the ischiocavernosus muscle and is composed of the albuginea *and Buck's fascia (incised and raised from the* spongy substance); *and a second* layer, superficial to the ischiocavernosus muscle, the major leaf of Colles' fascia and the crural septum arising from it.

6) Significance of the intercavernous septum of Buck's fascia. It has been shown in the previous paragraph that contrary to the condition on the urethra, where Buck's fascia retains constantly its individuality both in the shaft and in the perineal portion of the urethra, this fascia may fuse with the albuginea on the crura. There are however, cases in which Buck's fascia retains its identity also *on the crura*. Such a case is illustrated in figure 16 (479_{13f}, 1947, fig. 1) taken from the dissection of *the perineum of a* colored man, 64 years of age. *Cases* of this kind are especially suitable to obtain accurate information on the relation

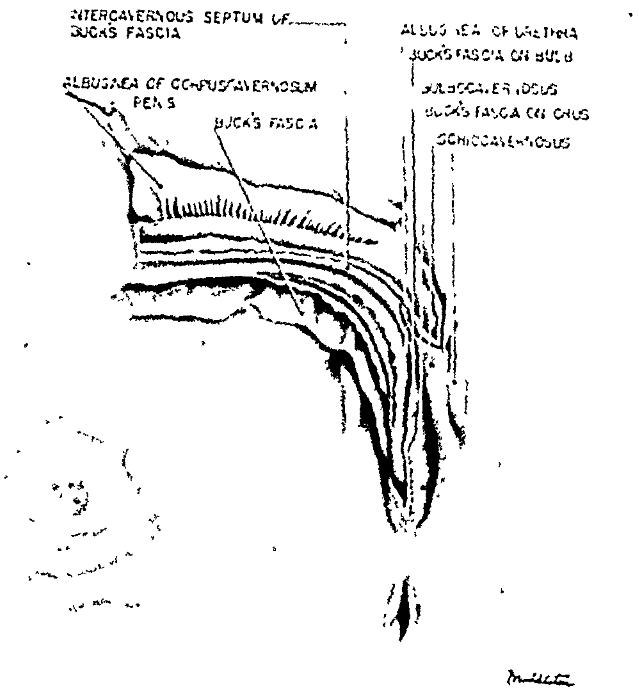

FIG. 16. Perineal dissection of Negro male (179, 1917, fig. 1), aged 64 years. A case in which Buck's fascia retained its individuality not only over urethra, but also over crura. Notice that bulbocavernosus as well as ischiocavernosus muscles lie superficial to Buck's fascia.

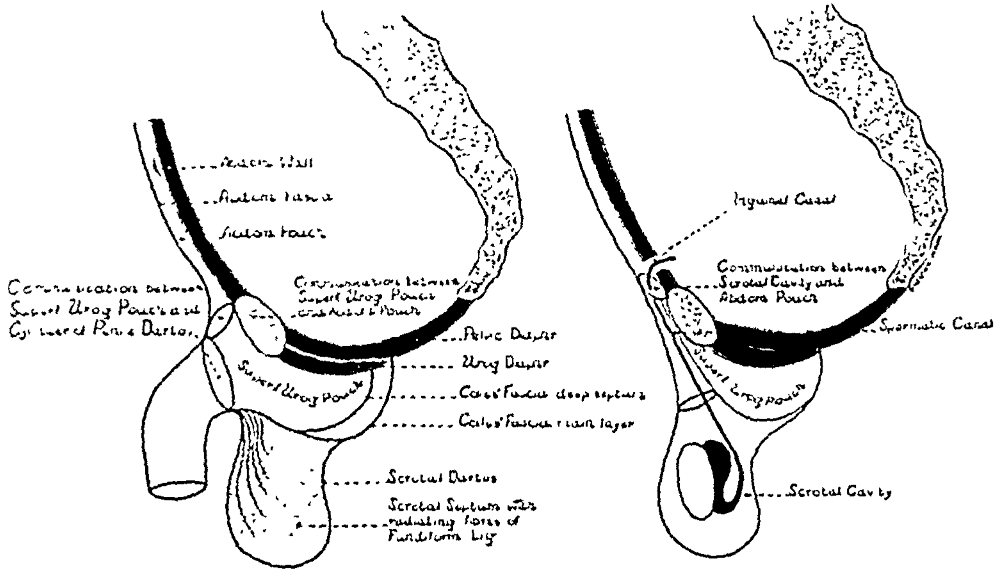
Abdom. Wall
Abdom. fascia
Abdom. Pouch
Communication between Superf. Urog. Pouch and Cylinder of Penile Dartos
Communication between Superf. Urog. Pouch and Abdom. Pouch
Pelvic Diaphr
Urog Diaphr
Superf Urog Pouch
Colles' Fascia deep septum
Colles' Fascia main layer
Scrotal Dartos
Scrotal Septum with radiating fibres of Fundiform Lig
Inguinal Canal
Communication between Scrotal Cavity and Abdom. Pouch
Spermatic Canal
Superf Urog pouch
Scrotal Cavity

FIG. 17. Sagittal section through perineum, *A*, along midsagittal plane; *B*, lateral to midsagittal plane. Showing communications of scrotal cavity and superficial urogenital pouch.

between Buck's fascia and the penile muscles. As may be learned from the illustration, both the bulbocavernosus and ischiocavernosus are superficial to Buck's fascia.

Moreover, this dissection shows plainly the nature of the intercavernous septum of Buck's fascia. This fascia exists in the perineum in the form of three separate cylinders, one which encloses the urethra and two which enclose the

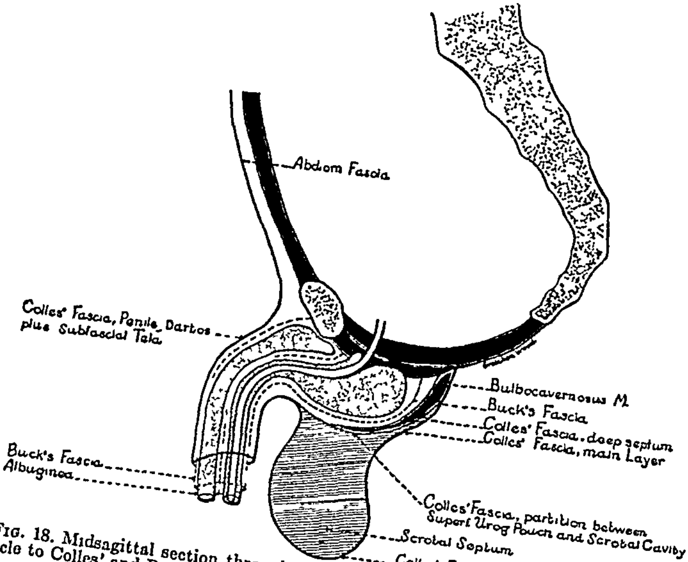
Abdom Fascia
Colles' Fascia, Penile Dartos plus Subfascial Tela
Bulbocavernosus M.
Buck's Fascia
Colles' Fascia, deep septum
Colles' Fascia, main Layer
Buck's Fascia
Albuginea
Colles' Fascia, partition between Superf Urog Pouch and Scrotal Cavity
Scrotal Septum
Colles' Fascia, Scrotal Dartos

FIG. 18. Midsagittal section through perineum, showing relations of bulbocavernosus muscle to Colles' and Buck's fasciae

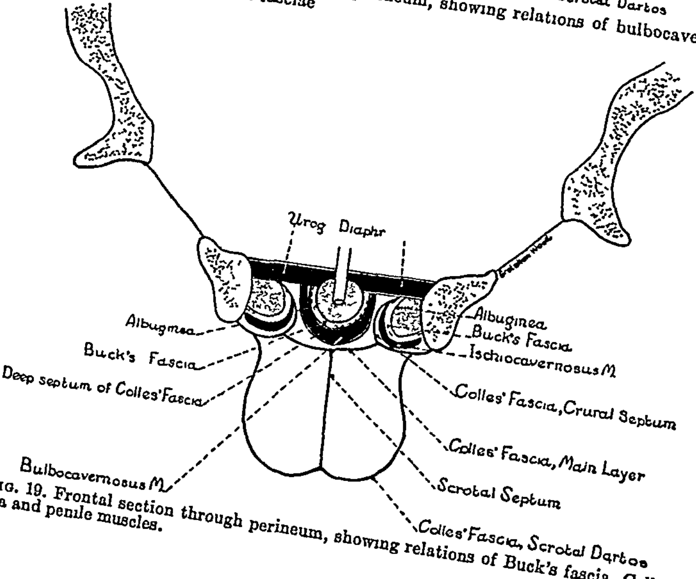
Urog Diaphr
Albuginea
Buck's Fascia
Deep septum of Colles' Fascia
Bulbocavernosus M
Albuginea
Buck's Fascia
Ischiocavernosus M
Colles' Fascia, Crural Septum
Colles' Fascia, Main Layer
Scrotal Septum
Colles' Fascia, Scrotal Dartos

FIG. 19. Frontal section through perineum, showing relations of Buck's fascia, Colles' ascia and penile muscles.

crura. The cylindrical envelop for the urethra extends as one continuous tube into the penile shaft as far as the corona. But the two crural cylinders fuse in the shaft to form one single cylindrical investment for both corpora cavernosa penis. Consequently in the shaft of the penis there exist only two such cylindrical envelopes. Where they are in contact with one another, their walls fuse together into the intercavernous septum of Buck's fascia as illustrated in figure 16.

IV. RECAPITULATION IN DIAGRAMS

Many diagrams, some of which we have reproduced in figures 1, 2 and 3, supposed to illustrate the relations of Colles' and Buck's fasciae, may be found in the literature. It is therefore appropriate that we show how such diagrams should look in our opinion and according to our findings. We recapitulate our observations in four diagrams illustrated in figures 17, 18 and 19. As they are provided with ample descriptions, there is no need to add any explanatory remarks here.

V. DISCUSSION

Our dissections show clearly the relations of Colles' and Buck's fasciae. On the free portion of the shaft of the penis both of these fasciae can be identified and kept apart with relative ease. Colles' fascia (penile dartos) can be traced without any interruption dorsally into the perineum; there it forms a partition (major leaf of Colles' fascia) between the cavities of the superficial urogenital pouch and the scrotum and also gives rise to the scrotal dartos. The leaf which forms the partition exhibits in no uncertain manner the chief characteristics described by Colles: it is firmly attached to the limbs of the pubic arch and lies superficial to the penile muscles.

Similarly Buck's fascia which on the shaft of the penis can be recognized by its intercavernous septum, by its aponeurotic nature and by its intimate adherence to the albuginea, can be dissected without any interruption both on the urethra and on the crura into the perineum; invariably, as the dissector follows this fascia, he is carried into a level deep to the penile muscles.

There exists no fascial space, either in embalmed or in fresh cadavers, between the albuginea and Buck's fascia; in fact it is difficult to believe that any exudate would be able to lift Buck's fascia off the albuginea and penetrate between these two layers. The fascial space lies between the fascia of Buck and Colles' fascia, both in the shaft of the penis and in the perineum; in the perineum, however, this space is divided by a deep septum and a crural septum of Colles' fascia into special compartments for the urethra and the crura, together with their respective muscles.

It is, moreover, obvious that on account of the presence of the partition formed by Colles' fascia, no direct anatomical communication can exist between the superficial urogenital pouch and the scrotal cavity. Both of these spaces are, however, connected with the abdominal fascial pouch (located between the superficial abdominal fascia and the external fascia of the external oblique aponeurosis, the latter to be described in another article); the scrotal cavity communicates with the abdominal pouch by way of the spermatic canals, the superficial urogenital pouch is open to the abdominal pouch in front of the symphysis pubis and lateral to the root of the penis. Hence an indirect communication via the abdominal pouch exists between the scrotum and the superficial urogenital pouch (see the diagrams in figures 17, 18 and 19).

The fact that the scrotal cavity and the superficial urogenital pouch are separated anatomically from one another does not necessarily mean that no urine can pass from the latter into the former. In a special article experiments will be discussed by one of us, the purpose of which was to test to which degree the partition of Colles' fascia is permeable for urine.

The question which will be in the minds of our readers will undoubtedly be the same that occupied the writers of this article. How can it be that two students who devoted most recently a special study to the re-investigation of the same structure which engaged our own interest, arrived at conclusions quite at variance with our own? In our opinion there can be only one answer to this question. Tobin and Benjamin must have taken for Buck's fascia, in the perineum, what is in reality Colles' fascia, and for the albuginea what was in reality Buck's fascia.

An inspection of figure 11 in the article by Tobin and Benjamin (see our fig. 6) will be of interest in this connection. The fascia which is labeled there with "Buck's fascia" is obviously the deep layer of Colles' fascia (Eberth's tela subfascialis). In the text these authors mention that at times Buck's fascia may become fused in the perineum with Colles' fascia, and their figure 11 is evidently an illustration of such a case. In our experience a fusion of these two fasciae, of the kind illustrated in figure 11 does not occur, whereas a fusion of the penile Dartos with the deep or subfascial layer of Colles' fascia is the rule and presents often the appearance it has in the specimen illustrated by Tobin and Benjamin. The real Buck's fascia is, however, actually visible in this figure 11 of Tobin and Benjamin (see our fig. 6), but is exposed only to a very slight extent, namely in the space between the right bulbocavernosus muscle and the cut margins of Colles' fascia.

The writers of the present article had an opportunity to listen to Doctor Tobin when he presented, at the recent anatomical meetings held in Madison, Wisconsin, his work on the fasciae of the perineum and abdomen. At this occasion he presented very beautifully colored lantern slides which showed an injection of the scrotal cavity with latex, made from the urethra into the scrotum and supposed to demonstrate how urine could enter the scrotal cavity in case of a tear or rupture of the penile urethra. The authors of this account do not deny, of course, that urine can actually pass from the superficial urogenital pouch into the scrotal cavity; but as will be shown by one of us in another article, the permeability of Colles' fascia for urine is restricted both with regard to the rate at which urine passes through this fascia and with regard to the maintenance of even this restricted rate of passage, circumstances which explain the delayed appearance of urine in the scrotum after rupture of the penile urethra.

Under these conditions it would be difficult to explain how materials of the consistency and size of particles, such as latex, could have passed through the partition formed by Colles' fascia. As we understand it the latex injections were made from the urethra into the scrotum. May it not have happened that with this technique the instrument used for the latex injections was passed not only through Buck's fascia but also through the fascial partition formed by Colles' fascia between the superficial urogenital pouch and the scrotal cavity?

SUMMARY

The perineum of 8 embalmed and 10 fresh male cadavers was dissected to study the relations of Colles' and Buck's fasciae.

Colles' fascia extends in one continuous sheet (major leaf) forward from the dorsal margin of the urogenital diaphragm, across the top of the scrotal cavity and becomes continuous, ventrally, with the abdominal fascia.

On its way forward Colles' fascia gives off the fascial wall of the scrotum (scrotal dartos) and, ventral to the scrotum, a cylindrical tube, the penile dartos.

Over the shaft of the penis Colles' fascia is separated from Buck's fascia by a deeper layer, Eberth's tela subfascialis.

In the perineum the major leaf of Colles' fascia gives origin a) to a "deep septum" which passes deep to the bulbocavernosus muscle, separates it from Buck's fascia and together with the major leaf of Colles' fascia, forms a fascial compartment for the bulbocavernosus muscle; b) to a "crural septum" which passes into the space between the bulb and the crus, becomes adherent to the crus just caudal to the inferior urogenital fascia and encloses the crus and ischiocavernosus muscle in a separate fascial compartment.

Buck's fascia extends from the corona of the glans penis over the urethra and bulb as well as over the crura. It lies deep to the bulbocavernosus and ischiocavernosus muscles.

There is no demonstrable space between albuginea and Buck's fascia, since the latter adheres firmly to the albuginea. The fascial space lies between Buck's fascia and Colles' fascia, both in the perineum and in the free shaft of the penis.

Since the major leaf of Colles' fascia stretches across the scrotal cavity and thus forms a fascial partition between the scrotal cavity and the cavity of the superficial urogenital pouch, there exists no direct anatomical communication between these two cavities (except in those cases in which this partition is perforated by slit-like openings).

Both of these cavities, however, communicate with the abdominal pouch, the scrotal cavity by way of the spermatic canals, the superficial urogenital pouch over the symphysis pubis.

The superficial urogenital pouch also communicates with the space between Buck's fascia and the penile dartos on the shaft of the penis.

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USE OF POLYMYXIN IN GRAM NEGATIVE URINARY TRACT INFECTIONS[1]

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Polymyxin, an antibiotic substance elaborated by Bacillus polymyxa, is active primarily against gram negative organisms[2, 3, 4, 5]. It is a white powder which is very soluble in water. An important feature of polymyxin is that the development of bacterial resistance to this antibiotic has not been demonstrated. This report is concerned with its therapeutic effectiveness and its limitations in cases of urinary tract infection.

Sensitivity to polymyxin of 78 strains of ten gram negative genera by the tube dilution method is presented in table 1. Polymyxin is markedly inhibitory for Salmonella, Shigella, Klebsiella, the Coli-Aerogenes species and, most importantly Pseudomonas. Brucella and selected strains of staphylococci are moderately sensitive while Proteus and hemolytic streptococci are refractory. The antibacterial action of the drug against Pseudomonas is not antagonized by the addition of subinhibitory amounts of streptomycin, penicillin, aureomycin or sulfadiazene. A strain of Pseudomonas, which developed high resistance to streptomycin in three daily transfers, showed no significant change in sensitivity to polymyxin after 27 daily transfers.

Polymyxin reaches the blood stream rapidly after intramuscular injection, and a therapeutically effective level is present within 30 minutes after administration. When a daily dosage of 2 to 4 milligrams per kilogram of body weight is given intramuscularly in divided doses, the blood serum concentration is 1 to 8 micrograms per milliliter. The peak level occurs 2 hours following injection. At 6 hours, one-half of the peak concentration is present, and at 12 hours, polymyxin is still measurable in the serum. When the drug is administered on a 6 hour schedule, the serum concentration is cumulative after 4 injections. In 1 patient given 4 doses of polymyxin on a 3 milligrams per kilogram basis, a blood serum level of 30 micrograms per milliliter was demonstrated. We have not noted a cumulative increase in serum levels when the drug is given only every 12 hours.

The excretion of polymyxin is primarily renal, and slower than that of penicillin and streptomycin. During the first 12 hours after injection of the drug, less than 0.1 per cent of the dose is recovered in urine. However, after 12 hours, a progressive increase in urinary excretion is found. When the daily dose is 3 milligrams per kilogram of weight, the output of polymyxin in the urine ranges between 40 and 400 micrograms per milliliter after 24 hours. A graphic illustration of the urinary excretion and serum levels in a patient is shown in figure 1. Assays were done by the tube dilution method. The urine was sterilized in preparation for assay by heating the specimen in a 60°C water bath for one hour. Zeitz or sintered glass ultra-fine filters cannot be used, since less than 1 per cent of the polymyxin passes through these filters. Heating the urine to 100°C for 10 minutes instead of 60°C for 1 hour results in loss of potency.

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TABLE 1. *Sensitivity to "aerosporin" polymyxin B*

ORGANISM	NO. STRAINS TESTED	SENSITIVITY RANGE IN MCGM./ML.	MEAN SENSITIVITY MCGM./ML.
Salmonella	5	0.08–0.3	0.18
Shigella	7	0.08–0.6	0.3
Klebsiella	5	0.16–1.2	0.48
Coli-aerogenes	17	0.06–1.6	0.8
Pseudomonas	19	0.3–3.1	1.2
Paracolobacter	2	1.2–1.6	1.4
Staphylococcus	6	1.2–5.0	2.0
Brucella	8	0.6–12.0	4.1
Beta hemolytic streptococcus	6	3(1)–>12.0	>12.0
Proteus	5	100–>100	>100
Total	78		

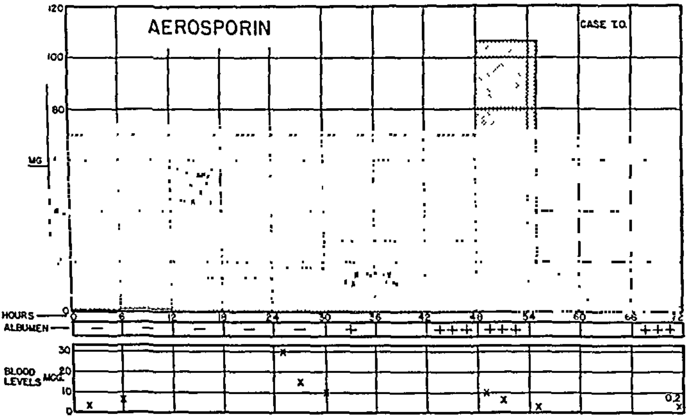

FIG. 1

When administered orally, none of the drug is detected in the blood. Polymyxin orally suppresses coliform organisms in 24 to 72 hours. Topical application of

1 per cent polymyxin in saline or carbowax base has resulted in the sterilization of several Pseudomonas aeruginosa-infected granulating wounds.

CLINICAL STUDY

Polymyxin therapy was evaluated in 20 cases of severe urinary tract infection. Eighteen patients received a single course of therapy with an average dose of 2.5 milligrams per kilogram of body weight per day administered intramuscularly, over periods ranging from 2 to 6 days. One patient was given only a single day of treatment coincident with which the urine became and remained sterile. Two patients were given second courses of therapy because cultures became positive 1 and 2 weeks respectively, after completion of the first course in treatment. Five of these patients had acute urinary tract infections with severe constitutional symptoms. The remaining 15 had long standing urinary tract infections, in some instances with acute exacerbations. In almost every instance, there was a history of chronic complicating factors including obstruction at various parts of the urinary tract, calculi, anomalies and postoperative residua. These patients, with only one exception (case 5), had had previous extended trials of other chemotherapy including penicillin, streptomycin, sulfonamides and others.

Both polymyxin B and polymyxin E have been tested.[6] These differ from each other in amino acid content and configuration.[7, 8] The antibacterial spectra are identical. The drugs which were supplied in sterile ampoules were prepared prior to injection by dilution with 1 per cent procaine so that each milliliter contained 25 or 50 milligrams. The drug was injected deep into the deltoid or gluteal muscles. Injection of polymyxin diluted with water or saline in lieu of procaine was attended by moderate to severe pain at the site of injection. The stability of the diluted drug under refrigeration is in excess of 8 weeks.

The dosage employed varied between 2 and 5.6 milligrams per kilogram of body weight per 24 hours and the average dose was 2.5 milligrams per kilogram. A few patients were given the calculated daily dosage at 12 hour intervals but this regime did not yield results as good as the 4 or 6 hour injection schedules. We consider the 6 hour schedule as satisfactory as the 4 hour schedule. The average *total* dosage given a patient was 10 milligrams per kilogram.

Urine specimens were cultured routinely prior to treatment, daily during and immediately following treatment and then weekly for 3 or more weeks. All specimens were cultured aerobically and anaerobically. Each bacterial species was isolated in pure culture and tested by tube dilution for polymyxin sensitivity. Routine and complete urological workup were carried out prior to treatment. Intake and output of fluids were recorded and maintained at normal levels.

ANALYSIS OF RESULTS

Improved groups. Ten of the 20 patients treated were regarded unequivocally as having been benefited by polymyxin therapy. Details of the cases are presented in table 2 In most instances, improvement was noted by the second day of treatment and was manifested by marked reduction or elimination of bacteria from the urine, regression of symptoms, decrease in fever and improvement in the urine as determined by complete urinalysis The outcome of treatment has been especially gratifying in acute Pseudomonas pyelonephritis cases

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[6] Kindly supplied by Burroughs Wellcome & Co., Tuckahoe, N. Y. and London.

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TABLE 2 *Cases benefited by polymyxin*

DIAGNOSIS	AGE	CULTURE SENSITIVITY MCGMS /ML.	DOSAGE MGM /MG /DAY	RESULTS
1 Contracted pyelonephritis with calculi, right chronic pyelonephritis with acute exacerbation left	40	Ps aeruginosa 1 6	3, 3 days Total 576 mgm	Sterile culture after 48 hours Marked symptomatic improvement
2 Minimal hydronephrosis, right severe residual post pyeloplastic (1945) hydronephrosis, left, further surgery refused	46	A aerogenes 0 4	2 5, 3 days Total 666 mgm	Sterile culture after 48 hours Marked improvement
3 Severe cardiac, acute pyelonephritis following TUR prostate	57	Ps aeruginosa 0 8	2, 3 days Total 480 mgm	Temperature normal and urine culture sterile within 48 hours
4 Acute pyelonephritis two weeks after right pyeloplasty, left pyeloplasty, 1947, results excellent	34	Coli intermed 0 06	2, 3 days 3, 3 days Total 750 mgm	Clinical improvement on first course sterilization urine on second
5 Right pyelonephritis three years acute episode two weeks	31	E coli 1 6	5 0 3 days Total 450 mgm	*Negative culture and urine after 24 hours Disappearance of cva pain*
6 Fulminating pyelonephritis with multiple cortical abscesses following endoscopic extraction of ureteral calculus decapsulation and nephrostomy	31	Ps aeruginosa 1 6	2 5 3 days 3 5 3 days Total 1500 mgm	Fever subsided by lysis Urine sterile and patient asymptomatic
7 Acute pyelonephritis right two weeks.	26	Para aerogenoides 1 6	3 3 days Total 425 mgm	Urine sterile after 48 hours CVA pain relieved 12 hours *after therapy begun*
8 *Acute* pyelonephritis right, and acute cystitis Gestation *seven months*	31	Coli intermed 1 6	3, 1 day Total 200 mgm	Urine negative, culture sterile patient asymptomatic
9 Residual pyelonephritis one month folowing pyelolithotomy	47	Ps aeruginosa 3 1 Para intermed 1 6	4 4, 3 days Total 900 mgm	Negative culture and urine, patient asymptomatic
10 Sacral defect with motor paralytic bladder no ureteral reflux postpyeloplasty for bilateral severe infected hydronephrosis, splinting *stage* Excellent surgical result	22	Ps aeruginosa 0 8	2, 3 days 4, 2 days Total 875 mgm	Sterile culture and improvement in urine

A 57 year old man who underwent a transurethral resection for benign prostatic hypertrophy developed acute pyelonephritis approximately 48 hours after surgery. A pure culture of Pseudomonas aeruginosa was grown from the urine. Polymyxin therapy was begun at the peak of the fever. The patient was converted

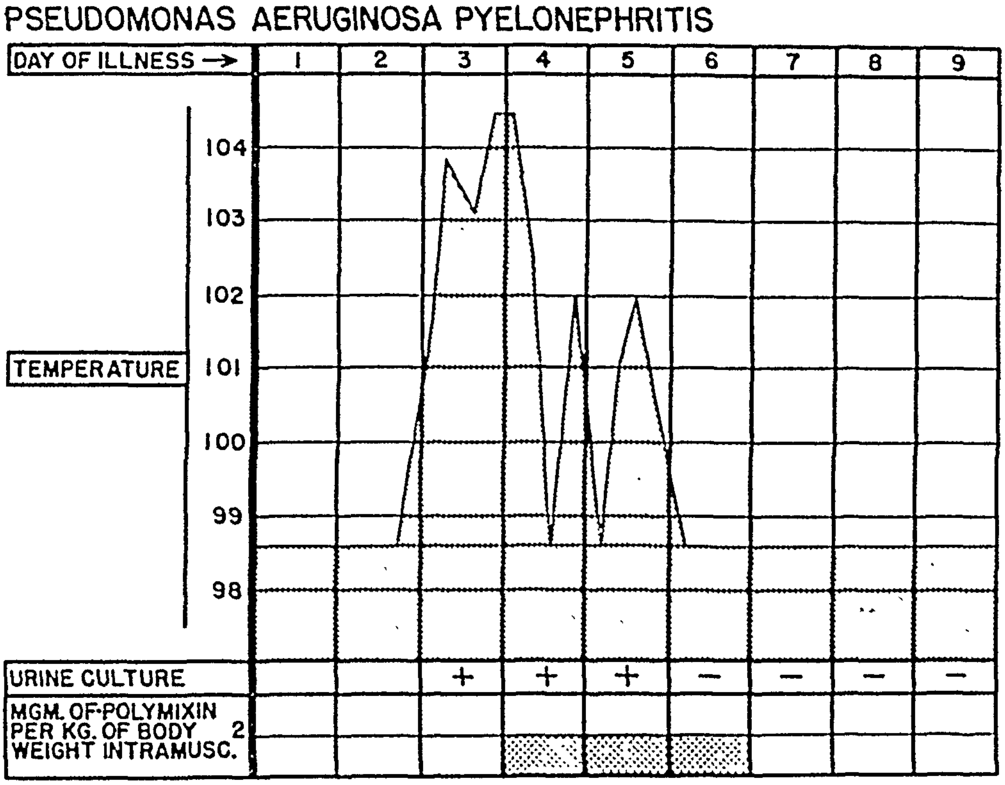

FIG. 2

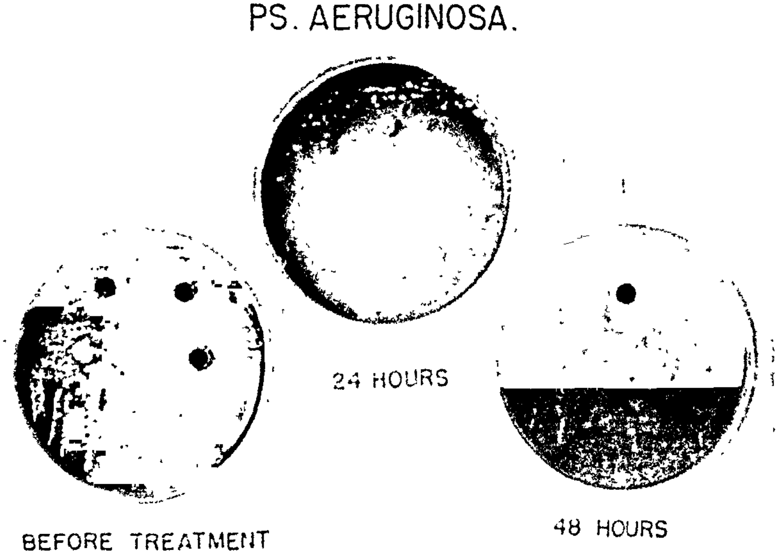

FIG. 3

from a critically ill status to a controlled infection within 12 hours after beginning polymyxin. In figure 2 is portrayed the response to treatment. Figure 3 is a photograph of the urine culture plates, and shows the elimination of the organisms at 48 hours.

TABLE 3. *Cases with doubtful results*

DIAGNOSIS	AGE	CULTURE SENSITIVITY MCGMS./ML.	DOSAGE MGM./KG./DAY	RESULTS
11 Severe chronic cystitis, self catheterization four years. Cystolithotomy and TUR prostate, 1948 Residual urine 40 cc.	77	E coli: 0.2	2, 3 days 4, 2 days Total. 600 mgm.	Sterile culture after 72 hours with slight improvement in urine and decrease in symptoms.
12. Chronic cystitis with vesical neck contracture, many years duration.	84	A aerogenes: 1 6	2, 3 days Total: 438 mgm.	Sterile culture with improvement in urine but no decrease in symptoms.
13 Severe left, chronic pyelonephritis, previous bilateral nephrolithotomy. Right calculous suppurative pyelonephritis with nephrolithotomy, 1948 Small calculi still present, right.	47	Coli intermed.: 0 4 Proteus. Resistant	3, 3 days Total 600 mgm.	Sensitive organism gone after 24 hours but proteus persisted Urine improved and symptoms decreased.
14. Bilateral pyeloplasty for severe hydronephrosis, initial failure, right, with second operation. Treatment during splinting period.	5 mos.	Ps. aeruginosa: 1 6 Coli intermed : 0 4	3, 10 days Total: 340 mgm.	Sterile urine left kidney. Right kidney contained persistent pus. Temperature became normal and was controlled
15 Acute pyelonephritis following TUR prostate	69	Ps aeruginosa 0.3-3 1	2, 6 days Total: 900 mgm	Temperature normal and urine sterile within 48 hours. Negative urine one week, then recurrence of organisms but not symptoms Treatment for residual urine followed by urine sterilization.
16. Double kidney and ureters, upper infected hydronephrosis and hydroureter secondary to ureterocele No response to drainage	46	Ps aeruginosa 3 1 Coli intermed 1 6	4, 3 days Total: 600 mgm.	Urine sterile and improved in 48 hours Negative urine for one week after treatment, then return of Coli but not Ps organisms
17 Multiple, bilateral, renal and ureteral calculi removed 1948 Severe hypertension Bilateral chronic pyelonephritis 4 mm calculus still present	56	A. aerogenes. 1 6	2, 6 days Total: 900 mgm	Clinical improvement symptomatic and in urine but persistent pos cultures

In all patients considered benefited by polymyxin therapy, improvement has been sustained for a minimum period of 3 weeks' follow-up. It is of interest that the causal bacteria in all instances were resistant in vitro to penicillin, streptomycin and sulfadiazene.

Doubtful cases. In 7 instances the results of polymyxin therapy were listed as being doubtful (table 3). Four patients had an immediate clinical and bacteriological response with elimination of organisms from the urine. Two of these 4 patients (cases 11, 12) have had no recurrence of organisms, but permanent improvement in the urine and decrease in symptoms were not considered sufficient to consider the results as good. The other 2 cases showed good immediate response (cases 16, 15), but had a recurrence of organisms within one or two weeks after withdrawal of drug. The bacteria did not become drug fast. Cases 13, 14 and 17 showed significant clinical improvement but resistant organisms persisted in the first and cultures remained positive in the latter two. Each of these patients had severe, long-standing pyelonephritis.

In 3 patients, treatment was regarded as an outright failure (table 4). One patient (case 19) had a Proteus infection. These organisms are known to be refractory to polymyxin. Another patient with bilateral long-standing pyelonephritis (case 18), had a sterile culture and negative urine after 24 hours' therapy. Her symptoms disappeared, but she relapsed in the next 2 weeks. The patient was given another course of polymyxin with the same immediate result, but the organisms reappeared 3 weeks later without symptoms. This case represents the scarred kidney with muliple cortical foci of infection. The third failure (case 20) was a patient with mixed gram negative infection complicating a far advanced hydronephrosis, hydro-ureter, pyelonephritis and ureteritis. Two courses of therapy improved the urine but did not eradicate the bacteria. Three months later, a *nephro-ureterectomy* was performed. The specimen was a scarred kidney and contained countless cortical abscesses from which the causal organisms were isolated.

TABLE 4. *Cases not benefited by polymyxin*

DIAGNOSIS	AGE	CULTURE SENSITIVITY MCGMS./ML.	DOSAGE MGM./KG./DAY	RESULTS
18. Bilateral chronic pyelonephritis three years. Gestation three months.	37	Shig. paradys.: 0.2	2, 3 days 3, 2 days Total: 600 mgm.	Sterile culture after 24 hours with recurrence in 2 weeks. Again sterile 24 hours after treatment begun with recurrence 3 weeks.
19. Horseshoe kidney divided 1944. Bilateral pyelolithotomy, 1944, 1947 and right, 1948.	23	Proteus: Resistant	2, 6 days Total: 1200 mgm.	Resistant organism and sustained fever.
20. Filiform urethral stricture and old false passage prostate. Dilatation and TUR prostate, 1947. Chronic pyelonephritis and ureteritis, right.	56	A. aerogenes: 0.4 Proteus: Resistant	2, 6 days Total: 750 mgm.	Slight, temporary improvement in urine and symptoms. Nephroureterectomy revealed marked, chronic pyelonephritis and ureteritis.

UNTOWARD REACTIONS

None of the patients treated developed any of the usual drug sensitivity reactions. When the dosage did not exceed 2.5 milligrams per kilogram, there was no increase in the blood urea nitrogen or nonprotein nitrogen, nor was there any consistent evidence of nephrotoxicity in the form of tubular damage attributable to the drug. When the dosage exceeded 4 milligrams per kilogram (in one instance, 3 milligrams) parenchymal damage was usually produced as evidence by increased albuminuria, red cells, white cells, renal cells and inconstantly, granular casts. Oliguria and fixation of the specific gravity at a low level were not consistently demonstrated. Urinary abnormalities produced as a result of drug therapy disappeared within a week after the drug was withdrawn. One patient (case 10) who received a dose of 4 milligrams per kilogram developed a slight increase in blood urea nitrogen which returned to normal 48 hours after the drug was discontinued.

In practically every instance, neurotoxic phenomena were associated with polymyxin administration. These consisted of paresthesias and hypesthesias mainly about the face and scalp, mild dizziness and weakness. These symptoms usually began with the first dose and persisted throughout the course of treatment. There were no objective neurologic abnormalities. Neurotoxic symptoms disappeared in every instance within 24 hours after completing the course of treatment. Symptoms were not severe enough to warrant cessation of therapy in any case. Adrenalin, intravenous calcium or the "anti-histamines" did not relieve symptoms. Polymyxin B and polymyxin E are similar in their toxic effects.

DISCUSSION AND SUMMARY

Polymyxin treatment of gram-negative urinary tract infections and correlative laboratory studies have revealed indications and contraindications for its use. The most important action of the drug is against Pseudomonas and the Coli-Aerogenes groups of organisms. All strains of Pseudomonas aeruginosa and A. aerogenes which we have treated to date have been found polymyxin-sensitive. On the other hand, all Proteus strains isolated from human sources have been found resistant. The successes achieved in eradicating Pseudomonas aeruginosa as well as Coli-Aerogenes organisms from the urine indicate that polymyxin is a potent new urinary antiseptic. Its importance lies in the fact that, contrary to aureomycin and chloramphenicol (chloromycetin), it is effective in Pseudomonas infection. On the other hand, polymyxin is of no value in Proteus infections.

The fact that drug-fast bacteria were not produced by treatment is of obvious significance. Hence, patients may be given small doses of drug in several courses of treatment without fear of developing resistance to polymyxin.

Like other antibiotics, polymyxin is relatively ineffective in cases where there are large calculi, obstruction to drainage, other foci of infection or irreversible changes as found in advanced pyelonephritis with the scarred, contracted kidney and cortical abscesses deficient in blood supply. However, in these cases, the drug is useful in the control of acute exacerbations or before surgery and during the postoperative course.

Where a mixed infection is present and an ancillary chemotherapeutic agent is indicated, combined therapy may be employed. There is no contraindication to combining polymyxin with other antibiotics, sulfonamides or urinary antiseptics. The pH of the urine has not been an important factor in the effectiveness of polymyxin therapy.

TABLE 5. *Additional cases treated*

DIAGNOSIS	AGE	CULTURE SENSITIVITY	DOSAGE	RESULTS
		mcgms./ml.	*mg./kg/day*	
21. Acute pyelonephritis following TUR prostate.	74	Ps. aeruginosa: 3.1	2.5, 2 days Total: 400 mg.	Benefited. Sterile culture and normal temperature after 48 hours
22. Sustained fever following dilatation urethral stricture.	68	Ps. aeruginosa: 0.39	2.5, 3 days Total: 450 mg.	Benefited. Temperature in 24 hours. Sterile urine in 48 hours
23. Left, chronic pyelonephritis. Acute exacerbation after TUR prostate.	56	Ps. aeruginosa: 3.1	3, 3 days. Total: 650 mg.	Benefited. Sterile urine in 24 hours. Low grade fever five days
24. Chronic cystitis with acute exacerbation.	63	Ps. aeruginosa: 0.78 Proteus resistant.	2.3, 3 days Total: 360 mg.	Benefited. Urine improved and temperature normal. Proteus resistant
25. Acute cystitis.	58	Ps. aeruginosa: 3.1 E. coli 1.25	2.1, 3 days Total: 360 mg.	Benefited. Sterile urine in 48 hours. Symptoms relieved in 24 hours
26. Acute bilateral pyelonephritis.	20	E. coli 3.1	2.5, 3 days Total: 399 mg.	Benefited. Temperature normal in 12 hours. Bilateral flank pain disappeared in one day. Sterile urine in 48 hours
27. Acute pyelonephritis following TUR prostate.	55	Ps. aeruginosa: 3.1	2.5, 3 days Total: 630 mg.	Benefited. Temperature normal in 24 hours. Sterile urine in 72 hours
28. Acute bilateral pyelonephritis following repair of vesicovaginal fistula.	29	Ps. aeruginosa: 1.0 E. coli 1.2	2.5, 6 days Total: 550 mg.	Doubtful. Normal temperature in 36 hours with relapse after drug stopped. Urine clear until recurrence of fistula
29. Chronic posterior urethritis and cystitis.	26	Ps. aeruginosa: 3.1	3, 3 days Total: 630 mg.	Doubtful. Urine sterile in 24 hours. Bladder capacity increased with slight decrease in symptoms
30. Chronic posterior urethritis and cystitis following prostatectomy.	67	Klebsiella: 1.6	2.5, 3 days Total: 600 mg.	Failure. Urine sterile in 48 hours but relapse in one week
31. Crossed fused renal ectopia. Left, with hydronephrosis. Left urethral calculus removed?	30	Alk. fecalis: 0.625	2.5, 2 days Total: 300 mg.	Failure. No improvement after 48 hours. Other antibiotics reinstituted

The factors limiting the parenteral use of polymyxin are the neurotoxic effects and the nephrotoxic effects. Nephrotoxicity in the form of cortical damage becomes apparent usually only when the dosage of polymyxin exceeds 3 milligrams per kilogram of body weight per 24 hours. Urinary findings indicative of cortical damage persist less than 1 week after the cessation of therapy. Neurotoxic symptoms occur in almost every instance regardless of the dosage but disappear within 24 hours after cessation of therapy. There is some indication that certain batches of polymyxin E are relatively free from neurotoxic side effects. When polymyxin therapy is indicated, we have found that the optimal course of treatment consists of 2.5 milligram of polymyxin per kilogram per 24 hours in divided doses given every 4 to 6 hours for 3 days. Nephrotoxic effects are minimal or absent with this ceiling dosage.

ADDENDUM

Since the completion of the manuscript, we have treated an additional 11 patients with polymyxin E (Lot No. E A113). The data concerning these cases are presented in table 5. This study was conducted in the manner outlined above and the criteria used for the evaluation of results were the same as those used in the first 20 cases.

Seven patients were benefited by therapy, 2 had doubtful results and 2 cases were considered as failures.

Two of these patients receiving 3 mg. of polymyxin per kg. per 24 hours had a transient increase in albuminuria during treatment. In 5 cases, we were unable to study nephrotoxicity because of coincident renal disease. Four cases on a 2.5 mg. dose of polymyxin had no evidence of nephrotoxicity. We have not observed nephrotoxicity in patients receiving 2.5 mg. or less of polymyxin E per kg. per 24 hours.

Five of these 11 patients reported neurotoxic symptoms. These consisted of slight itching of the face. One patient reported slight, transient dizziness; but in every case, the drug was well tolerated.

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AUREOMYCIN: A CLINICAL AND LABORATORY STUDY OF ITS EFFECT IN URINARY INFECTIONS[1, 2]

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Aureomycin was reported in July 1948 by Dr. B. M. Dugger.[3] It is now available in yellow crystallin form dispensed in 0.25 gm. and 0.5 gm. capsules for oral administration.

We welcomed a study of its possibilities because we were encountering many strains of organisms which no known antibiotic or chemotherapeutic agent would inhibit. This was demonstrated in a study in which 44 per cent of 150 organisms isolated from patients with urinary infections were found to be resistant to streptomycin.

Streptomycin-resistant, and streptomycin-sensitive organisms were found in the proportions shown in figure 1. The resistant strains caused persistent and chronic infection and led us to an impasse. It was on this group of patients and their organisms that we made most of the tests of this newer antibiotic.

NATURE OF STUDY

Organisms isolated from patients with persistent infection were identified and sensitivity tests were made using streptomycin, mandelic acid, aureomycin, gantrosan, and chloromycetin. Seventy-two strains altogether were tested for sensitivity to aureomycin according to the method of Dornbush in pencillin assay broth. The concentrations which were represented in the titrations were 5 mcg./cc, 2.5 mcg./cc, and so forth, down to 0.02 mcg./cc of aureomycin. Since the aureomycin is inactivated rapidly in the test tube and in the body, it was decided that the earliest possible readings were probably the most accurate measure of the true sensitivity of the organism being tested. The organisms grew sufficiently well after 4 hours' incubation at 37 C. to make readings at this point. Therefore, these readings were made and recorded as the sensitivity of the organism.

Patients from whom these organisms were isolated were given aureomycin by mouth in a dosage of 0.5 gm. every 6 hours. Microscopic and cultural studies of the urine collected from these patients during and after treatment were made frequently. In patients whose urine remained cloudy with pus after one week of medication the drug was discontinued and considered a failure. Patients whose

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[1] Read at annual meeting, American Urological Association, Los Angeles, Calif., May 17, 1949.

[2] These studies were made at St. John's Hospital, St. Louis, Mo.

[3] Duggar, B. M.: Introductory paper, read before the Conference of Section on Biology New York Academy of Science, July 21, 1948.

treatment or observation was interrupted for one reason or another were not included in this study. An effort was made to obtain at least two negative cultures before the patient was considered recovered, one taken after the medication had been discontinued. It is recognized that since a much higher concentration may be present in the urine (average of 135 mcg./cc)[4] while the patient is on the drug than in the tissue, the negative urine culture may not be the true index of recovery.

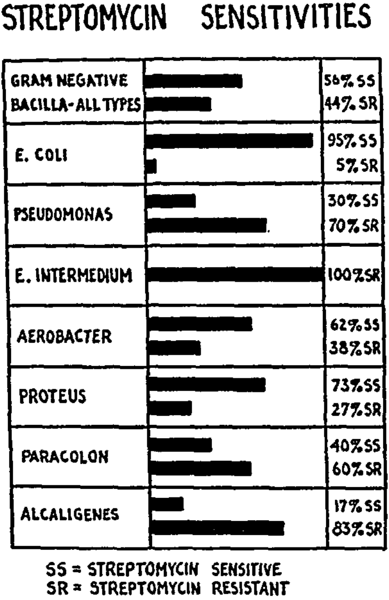

FIG. 1. Analysis of 150 gram negative organisms, indicating the high percentage of organisms resistant to streptomycin.

All urinary infections were taken consecutively without reference to the type of disease.

RESULTS OF STUDY

No serious effects of the drug were noted.

Nausea, probably due to acidity, was an annoying symptom in a high percentage of patients. This was relieved somewhat by administration of aluminum acetate hydroxide with each dose of aureomycin.

Diarrhea was noted in about 25 per cent of the patients, but was not a major complaint, being welcomed by many because of a previous chronic constipation.

The aureomycin sensitivity range of 72 organisms studied in this manner indicate that Escherichia coli, Escherichia intermedium, Aerobacter aerogenes, Paracolon, Alcaligenes, and Streptococcus fecalis are sensitive to aureomycin. The Streptococcus fecalis, the Escherichia intermedium, and the Aerobacter are highly sensitive.

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[4] Harrell, W. E. and Heilman, F. R.: Aureomycin: Studies on absorption, diffusion and excretion. Proc. Staff Meet. Mayo Clinic, 24: 157,166, 1949.

All the strains of Pseudomonas and Proteus examined were highly resistant to aureomycin, since it required 2.5 mcg. per cc or more to cause inhibition in the test tube. The aureomycin sensitivity range of organisms studied is represented in figure 2.

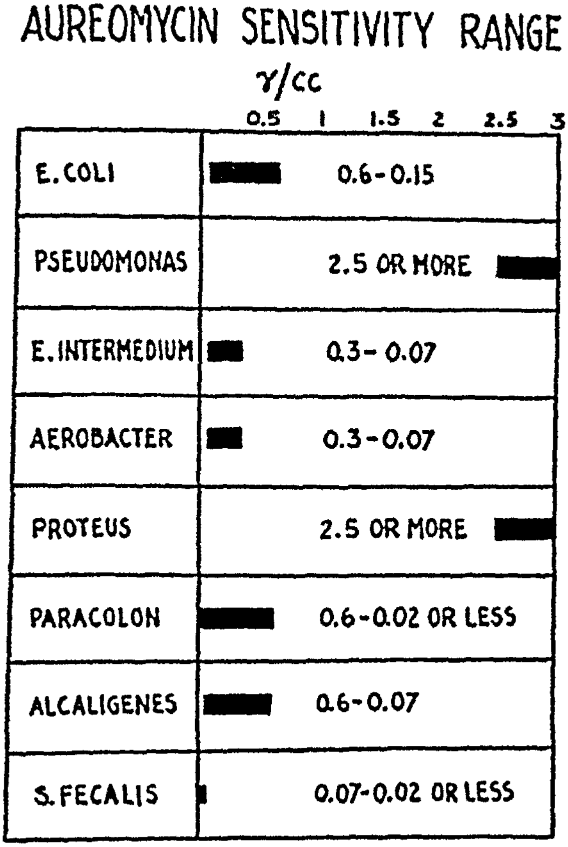

FIG. 2. Aureomycin sensitivity range of 72 organisms, indicating high susceptibility of Aerobacter aerogenes, the Escherichia intermedium, the Alcaligenes, the Paracolon, and Streptococcus fecalis. Pseudomonas and Proteus show high resistance in vitro.

IN VIVO STUDIES

Sixty-two patients were included in this study; for clarity the results are presented in two groups, one in reference to the organisms involved, the other grouped according to their diseases.

Of 6 cases of Aerobacter aerogenes with a sensitivity range in which the organism was not inhibited by 0.15 mcg. of aureomycin, but were inhibited by 0.3 mcg., 4 patients showed culturally clear urine, and the urine of 2 patients remained cloudy throughout the treatment.[5] Of 10 patients with Escherichia intermedium with a sensitivity range of 0.3 to 0.15 mcg. per cc, 9 showed recovery and 1 showed failure. Of 6 Escherichia coli with a range of 0.6 to 0.15 mcg. per cc, all responded with negative urines. Of 6 patients treated who had Paracolon with a sensitivity range of 0.3 to 0.15 mcg. per cc, all recovered and none failed to respond. Of 8 Streptococcus fecalis with a sensitivity range of 0.07 to 0.04 mcg. per cc, all 8 responded promptly.

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[5] One of these, a case of retropubic prostatectomy, became negative on continuation of aureomycin. The other patient, a case of left renal calculus, failed to respond.

Of 8 cases of Pseudomonas with a sensitivity range of 2.5 mcg. per cc or more, 2 responded and 6 were noted as failures. Of 4 Proteus cases with a sensitivity range of 2.5 mcg. per cc. or more, all four were failures. These results are noted in table 1, and show that the in vivo experience parallels the in vitro test fairly well.

TABLE 1. *Results of aureomycin treatment grouped in relation to organisms*

ORGANISM	NO. OF CASES	SENSITIVITY RANGE (MICROGRAMS/CC)	CULTURE NO GROWTH	CULTURE GROWTH
Aerobacter	6	0.3–0.15	4	2
Intermedium	10	0.15–0.07	9	1
E. Coli	6	0.6–0.3	6	0
Paracolon	6	0.3–0.15	6	0
S. Fecalis	8	0.07–0.04	8	0
Pseudomonas	8	2.5 mcg/cc+	2	6
Proteus	4	2.5 mcg/cc+	0	4

TABLE 2. *Results of aureomycin treatment following the transurethral operation*

PATIENT	ORGANISM	AUREOMYCIN SENSITIVITY (MICROGRAMS/CC)	DURATION OF TREATMENT *days*	RESULTS OF CULTURE
R. W.	Paracolon	0.6–0.3	7	Diminished
A. T.	E. Intermedium	0.15–0.07	13	E. Intermedium remains
	S. Fecalis	0.04–0.02		
M. P.	Paracolon	0.03–0.15	7	—
T. N	Paracolon	0.3–0.15	10	—
J S	S Fecalis	0.04–0.02	7	—
	B. Coli	0.15–0.07		
L. B.	Aerobactor Aerogenes	0.3–0.15	6	—
C. A.	Alcaligenes	0.15–0.07	5	—
O. A.	E. Intermedium	0.3–0.15	3	—
J. W.	E. Intermedium	0.15–0.07	10	—
W. H.	B. Coli	0.6–0.3	10	—

In order to visualize the effectiveness of aureomycin, we have grouped some of the patients according to diseases. Persistent pyuria had been the rule rather than the exception in our post transurethral patients before aureomycin. Aureomycin was given prior to and immediately after the operation, the Foley catheter removed on the third day. In 9 out of the 10 patients so treated, clear urine was obtained on an average of one week. The organisms isolated and their sensitivity range are recorded in table 2, which shows unusually favorable results obtained by aureomycin following transurethural surgery.

Of 10 patients having renal calculi treated post operatively there were 3 failures and 7 recoveries. Of the 3 failures, 2 were Pseudomonas. The details are noted in table 3. A different group of patients show fair results with aureomycin. The poor results are due to the Pseudemonas aeroginosa.

Nine patients were treated postoperatively with aureomycin who had undergone a retropubic prostatectomy. All of these were made culturally clear (table 4).

TABLE 3. *Results of aureomycin treatment in patients following operation for renal calculi*

PATIENT	ORGANISM	AUREOMYCIN SENSITIVITY (MICROGRAMS/CC)	DURATION OF TREATMENT	RESULTS OF CULTURE
			days	
E. K.	Pseudomonas	5 or more	10	+
	Aerobacter	0.15-0.07		
R. M.	E. Intermedium	0.3-0.15	10	−
M. A.	Aerobacter	0.15-0.07	6	−
M. P.	Paracolon	0.3-0.15	7	−
M. E.	Pseudomonas	5-2.5	13	+
K. K.	B. Coli	0.6-0.3		
	S. Fecalis		4	PS+
	Pseudomonas			
T. N.	Paracolon	0.3-0.15	7	−
M. T.	Aerobacter	0.15-0.07	4	−
J. W.	E. Intermedium	0.15-0.07	10	−
M. McM.	B. Coli	0.6-0.3	4	−

TABLE 4. *Aureomycin treatment following retropubic operation*

PATIENT	ORGANISM	AUREOMYCIN SENSITIVITY (MICROGRAMS/CC)	DURATION OF TREATMENT	RESULTS OF CULTURE
			days	
E. B.	E. Intermedium	0.3-0.15	7	−
F. B.	Paracolon	0.04-0.02	5	−
E. C.	Aerobacter	0.3-0.15	8	−
H. C.	B. Coli	0.15-0.07	7	−
T. C.	Aerobacter	0.3-0.15	4	−
R. R.	E. Intermedium	0.3-0.15	6	−
J. P.	E. Intermedium	0.15-0.07	6	−
E. B.	B. Coli	0.6-0.3	3	−
R. E.	Aerobacter	0.3-0.15	7	−

One patient having a radical prostatectomy with removal of seminal vesicles had clear urine 14 days after operation and aureomycin therapy.

There were 4 patients who had a nonspecific urethritis of long standing whose discharge disappeared within 3 days of treatment. In 3 cases the culture from the urethral discharge was negative. One case of Reiter's disease treated with aureomycin showed prompt improvement as shown by the disappearance of the discharge and the conjunctivitis. Although the arthritis subsided somewhat, it remained even though 2 weeks' treatment with aureomycin was given. More rapid improvement was shown when marphasen was given with the aureomycin.

Five patients with nonspecific prostatitis, chronic in nature, given aureomycin for 5 days showed disappearance of pus in the prostatic secretion. Insufficient data and number of patients treated make any statement unreliable in this type of case.

The question of development of resistance or emergence of resistance strains is a very vital one in practical therapy. Unfortunately, streptomycin has this unsatisfactory feature. This has not been a drawback in aureomycin therapy.

COMPOSITE IN VITRO SENSITIVITIES

	STREPTOMYCIN	NU	AUREOMYCIN	CHLOROMYCETIN
E. COLI	−	−	±	−
PSEUDOMONAS	+	+	+	± ?
E. INTERMEDIUM	+	+	−	−
AEROBACTER	±	+	−	−
PROTEUS	±	−	+	−
PARACOLON	±	±	−	−
ALCALIGENES	±	−	±	−
S. FECALIS			−	−

+ = RESISTANT
− = SENSITIVE
± = SOME RESISTANT, SOME SENSITIVE

FIG. 3. This chart indicates that NU-445 is useful in E. coli, Proteus and Alcaligenes. Aureomycin is of no value in Proteus, but is of value in Aerobacter aerogenes, Escherichia intermedium and Streptococcus fecalis. Chloromycetin useful in most except Pseudomonas.

SENSITIVITY SUMMARY

	STREPTOMYCIN	NU	AUREOMYCIN	CHLOROMYCETIN
E. COLI	±	−	−	−
E. INTERMEDIUM	+	+	−	−
AEROBACTER	±	+	−	−
PSEUDOMONAS	±	+	+	+
PROTEUS	±	−	+	−
PARACOLON	±	±	−	−
ALCALIGENES	±	−	−	−
S. FECALIS		+	−	−

+ = RESISTANT
− = SENSITIVE
± = SOME RESISTANT, SOME SENSITIVE

FIG. 4

We have noted an increase in resistance in only one instance and this was observed in a clinical case of Escherichia intermedium.

Recurrences of infection and cloudy urine occurred in some of these patients who are shown as having culturally clear urines and therefore they are not reported as cures. This only indicates that one urinary antiseptic cannot cure all urological infections, but can assist the urologist in relieving the pathology and obstructions which cause infections.

SUMMARY

Sensitivity tests have been made with aureomycin on 72 gram negative bacilli and Streptococcus fecalis. Patients from whom these organisms were isolated were given 2 gm. daily of aureomycin and periodic microscopic and cultural studies were made of the urine.

The results of these observations would indicate that aureomycin is effective in urinary infections where the infecting organism is identified as Escherichia coli, Escherichia intermedium, Aerobacter aerogenes, Paracolon, Alcaligenes, and Streptococcus fecalis. Pseudomonas and Proteus infections were observed to be resistant both in vivo and in vitro. It compares favorably with other antibiotics and chemotherapeutic agents (fig. 3). Nausea and diarrhea were prominent symptoms while the drug was being taken but no serious toxic effects were noted.

Our overall study of antibiotics and chemotherapeutic agents would indicate that no one agent will be effective in all infections but that successful treatment depends on the identification of the organism and the selection of the agent to which the organism is sensitive (fig. 4). The Pseudomonas still remains the most resistant and persistent.

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CHLOROMYCETIN IN THE SUCCESSFUL TREATMENT OF RECURRING EPIDIDYMITIS[1]

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This paper deals with a remarkable new antibiotic used in treating the most troublesome genital infection in the whole field of urology.

Chloromycetin (chloroamphenical, *Parke-Davis*) a pure crystalline substance was discovered by Paul Burkholder at Yale after screening several thousand cultures.[2] Bartz[3] isolated the pure crystalline form from the culture broth and finally Cooks[4] et al. produced the drug synthetically.

Chloromycetin is nontoxic, can be administered orally up to 100 mg. per kilo body weight, with an average initial dose of 50 mg. per kilo. This means 3 gm. divided into 1 gm. or four $\frac{1}{4}$ gm. capsules each hour for 3 hours; then $\frac{1}{4}$ gm. every 3 hours. The drug is rapidly absorbed from the gastro-intestinal tract and about 10 per cent is eliminated from the urine. The above dosage produces a steady flow of 80 millimicrons of drug in the urine per hour which is highly bacteriostatic. Although slightly soluble in water it can be injected parenterally in 8 per cent solution of propyl glycol—the instructions being to inject slowly (3 minutes for 10 cc). This drug has been found to be effective against an impressive range of micro-organisms: enteric infections, notably typhoid[5] and other *Salmonella types; diseases in which the rickettsias are etiological factors,*[6, 7] and virus infections including atypical pneumonia, psittacosis, lymphogranuloma venereum, and many others with finally bacillary urinary infections against which chloromycetin can be depended on to be a rather startling therapeutic factor.

At Puerta Acosta, Bolivia, 14,000 feet elevation during a typhus outbreak, Payne and Knandt[6] aided by the local doctor, Dr. S. Palacios, obtained striking cures virtually snatching from death several typhus cases with rapid intravenous therapy. One patient in particular with paralyzed mouth and left side, who had no nourishment in 3 days regained consciousness and was able to speak after the first injection. In 22 cases all symptoms were relieved in an average of 50 hours after Chloromycetin was started.

Chloromycetin will terminate the fever of acute brucellosis in an average of

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[1] Read at annual meeting, American Urological Association, Los Angeles, Calif., May 17, 1949.

[2] Ehrlich, J., Gottlieb, D., Burkholder, P. R., Anderson, L. E. and Pridham, T. G.: Streptomyces venezuelae—the source of Chloromycetin. J. Bact., 56: 467, 1948.

[3] Bartz, Q. R.: Isolation and characterization of Chloromycetin. J. Biol. Chem., 172: 445–450, 1948.

[4] Crooks, H. M. Jr., Bartz, Q. R., Rebstock, M. C., Long, L. M., Controulis, J. and Troutman, H. D.: Synthesis of chloromycetin. Read before Am. Chem. Soc., San Francisco, March 29, 1949.

[5] Woodard, T. E., Smadel, J. F., Ley, H. L. Jr., Green, R. and Mankikar, D. S.: Beneficial effect of chloromycetin in the treatment of typhoid fever. Ann. Int. Med., 29: 131, 1948.

[6] Payne, E. H., Knaudt, J. A. and Palacios S.: Treatment of epidemic typhus with Chloromycetin. J. Trop. Med. & Hyg., 51: 68, 1948.

[7] Pincoffs, M. C., Guy, E. G., Lister, L. M. and Woodard, T. E.: Treatment of Rocky Mountain spotted fever with Chloromycetin. Ann. Int. Med., 29: 656–663, 1948.

2.4 days, in specific against the colon group in urinary infections as well as against Aerogenes, Pseudomonas, Klebsiella, Salmonella and Proteus. This drug is up to 36 times as active as penicillin against tested gram negative bacteria but only one-tenth as active against gram positive cocci such as Staphlycoccus aureus although in atypical pneumonia its acts as a specific.

As you may very well surmise, Chloromycetin will clear up bacillurias in a remarkably short time and 0.25 gm. should be continued every 3 hours by mouth for 7 or 8 days after the urine is cleared up. Even then secondary cocci invaders may crop out especially in presence of malignancy, calculi, urine retention and pathological anomalies. Where such anomalies do not exist and cocci appear, penicillin is indicated as an adjunct to chloromycetin therapy.

And speaking of pathological anomalies, we are herewith reporting 5 cases the pathology of which has always been troublesome. Epididymitis strikes out of a clear sky. The literature is full of traumatic types producing epididymitis, nonspecific too, and with urethra normal. Many writers now believe the offenders are the seminal vesicles, the ampulla, the vas and ejaculatory ducts though Young,[8] McCarthy,[9] Cabot,[10] Caulk,[11] Belfield,[12] Ritter,[13] and Herbst[14] have shown that the pathology of the seminal vesicles has not received the attention it deserves. Indeed Gonzales-Iman [15] stated in 1943 that seminal vesiculitis is not a closed chapter. "This clinical and physical entity offers many problems that are far from being solved." He catheterized 898 ejaculatory ducts and found he could catheterize only one of the sides in about half the cases. There were 13 per cent normal vesicles, catarrhal infection 65 per cent, healed vesicles 16 per cent. Thus 81 per cent of all vesicles studied either were or had been infected! Gonzales-Iman continues: "There is a type of patient, usually between 30 and 50 years of age, who has gone to a private physician for his 'prostate gland' being treated with a series of dilatations, sounds, massages and frequently some form of instillations. The symptoms of these patients vary, but the most common complaints are of a drawing dull pain in their rectum, perineum, or glans penis, backache, pain in the groin, hip, or leg, sexual asthenia, functional impotence, hemospermia, premature or involuntary ejaculations, sometimes associated with pain in the joints etc., with more or less typical symptoms of chronic posterior urethritis. Usually the patient asks if he is ever going to get well. If a quick examination is made, a diagnosis of chronic prostatitis or posterior urethritis is probable meaning more sounds and massages and administration of a sulfa drug. If such a patient fails to improve he may either be discharged or passed along to a psychiatrist who, in turn, may find him neurotic."

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[8] Young, H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926, vol. 1, p. 166.

[9] McCarthy, J. F. and Ritter, J. S.: The seminal vesicles: Newer instrumental methods in diagnosis and therapeutic management. J. A. M. A., 98: 687, 1932.

[10] Modern Urology, edited by H. Cabot. Philadelphia: Lea & Febiger, 2nd ed., vol. 1, p. 326.

[11] Caulk, J. R.: Surgery of the Seminal Vesicle and Ducts. Essay.

[12] Belfield, W. T.: Vasotomy radiography of the seminal duct. J. A. M. A., 61: 1867, 1913.

[13] Ritter, J. S. Diseases of the Seminal Vesicles. Davis Encyclopedia of Med. Spec., 13: 814, 1939.

[14] Herbst, R. H. and Merricks, J. W.: Visualization of seminal vesicles. J. Urol., 41: 739–750, 1939.

[15] Gonzales-Iman, F.: Retrograde vesiculography, J. Urol., 49: 618, 1943.

However, urologists by routine rectal examination in many cases with palpation, massage, and study of expressed secretion can determine the extent of seminal vesicle as well as prostate involvement. But we run across cases all of the time in which such examinations reveal nothing. In many cases the seminal vesicles are not examined at all. Young stated that Dillon and Blaisdell[16] had supplied the only systematic study that had existed up to that time. McCarthy[9] and many others have offered x-ray studies of catheterized ducts and vesiculograms that clearly demonstrate pathological changes in the genital tract. Hinman[17] has coined the term "prostato-vesiculitis" (fig. 1).

But the literature is replete with cases of routinely treated prostates with indications of recurring symptoms and absorption pointing to the seminal vesicles as the site of focal infection. And with protracted treatment, as Gonzales-Iman[15] pointed out, in such a case neurasthenia may develop. Yet why, when men are considered in perfect health like the cases reported by Wofendale[18] and and Edwards[19] one lifting one end of a piano, the other slipping on a rug and attempted with sudden muscular effort to prevent falling, why do they both develop acute epididymitis? Given a low grade, unsurmised infection of the seminal vesicles and ducts as well as a condition simulating a cord bladder, and we have the answer. With a sudden so called "strain" placing as much as 50 pounds' extra pressure on the partially filled bladder with the internal sphincter giving way, and external sphincter still in a spastic state, the transmitted hydrolic pressure forces urine into the ejaculatory duct, passing through the ampulla on down to the globus minor, the urine carrying with it infection from pathological changes above. Why does the urine pass into only one duct in 90 per cent of the cases? Because, as discovered by those who have attemped to catheterize

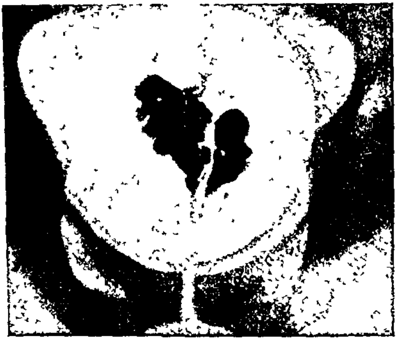

FIG. 1 Note poor filling of left seminal vesicle because of chronic infection.

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[16] Dillon, J. and Blaisdell, C. B Surgical pathology of seminal vesicles. Calif. State Med Jr , 18: 149, 1920

[17] Hinman, F.. Principles and Practice of Urology. Philadelphia: W. B. Saunders Co., *1935, p. 817.*

[18] Wolfendale, G. A. Acute epididymitis due to muscular strain. Brit. Med. J , 1: 808, 1913

[19] Edwards, A. Acute epididymitis produced by muscular strain. Brit. Med. J., 1: 833-834, 1912.

chronically infected ducts, the patency is very seldom the same in the two ducts, i.e., one duct is patent, the other usually not, as Gonzales-Iman pointed out.[15] So the urine, if not infected before, becomes infected on its way and quickly produces epididymitis on one side. McCarthy, from a great series of autopsy studies, has shown the percentage involvement of the ducts, seminal vesicles, and epididymes.

We cannot take the time here discussing the pathology of epididymitis; but we should keep in mind that infection by direct extension through the vas and lymphatics involves the globus minor; whereas certain blood stream infections like syphilis, typhus, meningitis, and malaria affect the globus major; and metastatic infections like typhoid, variola, brucellosis and filariasis attack the testes.[20] On injecting the vas either throught an urethroscope into the ejaculatory ducts or by puncture of the vas below the external ring, the seminal vesicles and apulla always become injected (fig. 2). Therefore any low grade infection in these "male pus tubes" that have the poorest drainage of any cavity in the body[21], will be carried to the epididymis both by urinary backflow and by way of the lymphatics.

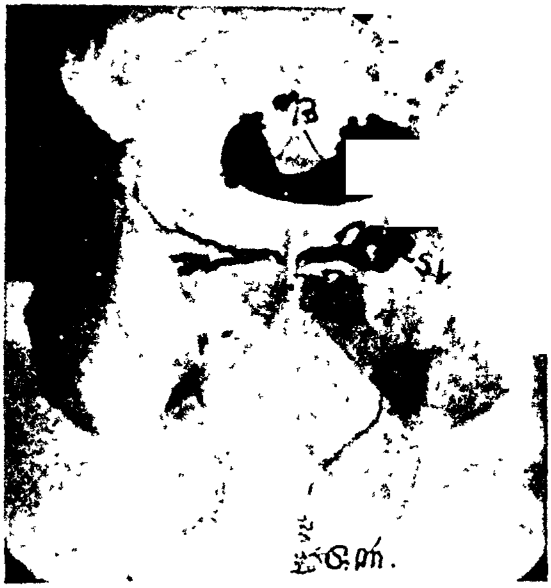

FIG. 2. Depicts complete injection from ducts to globus minor. *G. M.*, globus minor; *S. V.*, seminal vesicles; *D*, duct; *B*, overflow of injection fluid into bladder.

One of the problems that interests us here is can Chloromycetin check the epididymitis that may follow prostatectomy? Alyea[22] wrote in 1928 that Frontz and Colston of the Johns Hopkins Hospital, since 1927 have routinely performed vasectomy before removing the prostate to prevent attacks of epididymitis, that occur in 15 per cent of all cases when vasectomy is not done. Alyea also points out that even with vasectomy 4 per cent of the cases develop epididymitis anyway We mentioned 3 years ago[23] that, with the drainage tubes, catheters, as well as in any type of stasis, when using streptomycin to clean up the flora of the genito urinary tract, that drug will develop a fastness and should not be used in such cases But with Chloromycetin, using, say 3 gm as an initial dose, there is a constant excretion of 80 millimicrons for over 24 hours, then with a maintenance dose of ¼ gm by mouth every 3 hours, whether you have a retention catheter or drainage tubes, this drug used pre- and postoperatively should prepare your patient for such an eventuality Remember, operators doing radical surgery of the colon for cancer have no vas to ligate to prevent postoperative complications, so, like McNealy and Wolfe[24] they say "If the bowel can be decompressed by enemas, chemical biostatics will reduce the bacterial flora to a level compatible with urinary healing " Implementing penicillin to take care of gram positive cocci together with Chloromycetin to keep the tract clean of all other of the commoner pathological bacteria, and with no danger of fastness developing, even with catheters and drainage tubes present, it is quite possible such use of these drugs will eliminate the necessity of vasectomy before prostatectomy is performed

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[20] Luys, G.: Le cathéterisme des canaux éjaculateurs. Clinique, Paris, 23: 73, 1928.

[21] Kaufmann, H. K.: Lehrbuch der Speziellen path. Anat. Berlin: 1922, ed. 8, pp. 1186–1188.

[22] Alyea, E. P.: Vaso-ligation a preventive of epididymitis. J. Urol., 19: 65–80, 1928.

CASE REPORTS

Case 1 R A , aged 35, 5 feet 8 inches, weight 152 pounds, had never been sick in his life, had mumps of the left testicle with parotiditis both sides of the face The temperature was 103 5 F The condition of testicle was most troublesome Using 60 mg Chloromycetin per kilo of body weight, about 4 gm initial dose, broken into 4 capsules each hour for 4 hours, and then 1 capsule was given every 3 hours In 12 hours all pain left the testicle, and in 20 hours after starting Chloromycetin the patient became afebrile In 26 hours after starting Chloromycetin no symptoms or signs existed in the neck or scrotum He became ambulatory the third day after treatment

Case 2 C W , white, aged 38, height 5 feet 11 inches, weight 175 pounds, had had gonorrhea 12 years previously, followed by recurring epididymitis He came to us with the fifth attack of epididymitis in 2 years, and he claimed that the epididymitis followed a "strain " The history of each attack was about the same While doing heavy lifting with the bladder partly filled with urine he would suddenly develop a sharp stabbing pain in the left testicle followed by epididymitis that would remain painful and swollen for 2 weeks Except for the attacks of epididymitis that were crippling and frightfully painful, the patient had always been well Examination showed swelling and tenderness in the left side of scrotum involving the epididymis The temperature was 101 5 F The attack of epididymitis started the day before admission The urine showed coli, Friedlander and Proteus We gave him 1 gm Chloromycetin every hour for 4 hours and then ½ gm every 3 hours by mouth In 36 hours all pain disappeared and swelling was reduced by one half In 48 hours all swelling had disappeared

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[23] Redewill, F H Streptomycin in the successful treatment of tuberculosis of the urinary bladder J Urol , 58 35–46, 1947

[24] McNealy R W and Wolfe, F D Operation in carcinoma of the left half of the lower bowel Am J Surg , 76 646–648, 1948

We examined the verumontanum before and after treatment; the comparison is shown in figure 3.

Case 3. A. B., aged 41, white, height 5 feet 9 inches, 160 pounds weight, had been treated by us twice before for similar attacks. His attack always seemed to follow a "strain" of heavy lifting. Examination between attacks revealed a coccal and staphylococcal infection of the seminal vesicles and prostate. Besides routine treatment he was put on sulfa drugs and penicillin, but he did not continue treatment long enough to become cured between attacks. At his last attack, February 1, 1949, we examined his posterior urethra during and after the last attack (fig. 4). He was given 1 gm. of Chloromycetin in broken doses and ¼ gm. thereafter every 3 hours by mouth. Neither he nor any of the other patients showed any toxic effect from the drug. Because he had staphylococcus aureus infection as well, we gave him procaine penicillin 300,000 units intramuscularly daily. It is definitely understood that Chloromycetin is 10 times weaker than penicillin against that particular coccus so we used the synergistic action of the two drugs. He had no pain the next day, became afebrile and the swelling disappeared in 2 days. The two drugs were continued 7 days longer. Then the secretion from the seminal vesicles and urine was free of any bacteria.

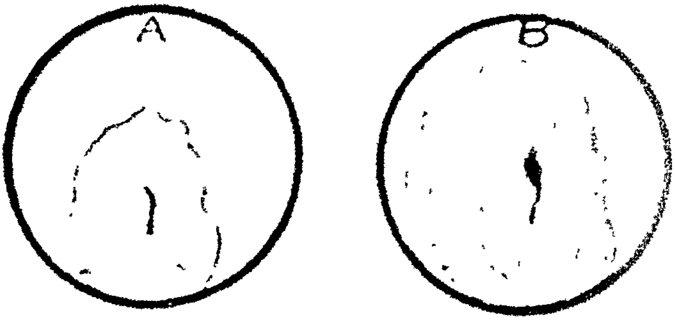

Fig. 3. Case 2. *B*, appearance of verumontanum during attack; *A*, appearance of verumontanum after treatment with Chloromycetin.

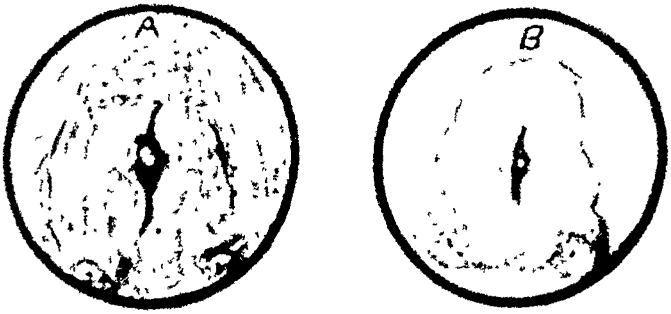

Fig. 4. *A*, appearance of verumontanum during attack; *B*, appearance of verumontanum after treatment with Chloromycetin.

Case 4. E. H. K., aged 25, height 5 feet 10 inches, weight 153 pounds, had a neisserian infection 4 years previously. During the last 2 years he had 3 attacks of epididymitis on the left side and reported to us the last time on January 14, 1949. After the attack 1 year ago, on urethroscopic examination and injection of the left ejaculatory duct with Diodrast, we found it patent to the globus minor, and a dilated seminal vesicle that filled poorly Streptomycin and sulfadiazine were given for the attack at that time He did not continue treatment long enough to clear up his infection last year On January 14, 1949 organisms present were gonococci and coli

Here is a case like many reported in the literature, and by Crane in particular,[25] who collected 9 cases of so called 'strains,'' with the gonococcus the etiological factor On January 13 the patient was lifting some heavy pipe for a construction company and suddenly a severe pain was felt in his left scrotal sac On January 14 the epididymis was very large and painful The temperature was 102 5 F He was placed on 3 gm Chloromycetin and then ½ gm every 3 hours During this attack the urine and slides showed gonococci and colon bacilli The infection cleared up solely on Chloromycetin in 50 hours, and the drug was continued for 10 days Final examination revealed no bacilluria and normal seminal vesicles and prostate It is unlikely that the patient will have any more so called "strain "

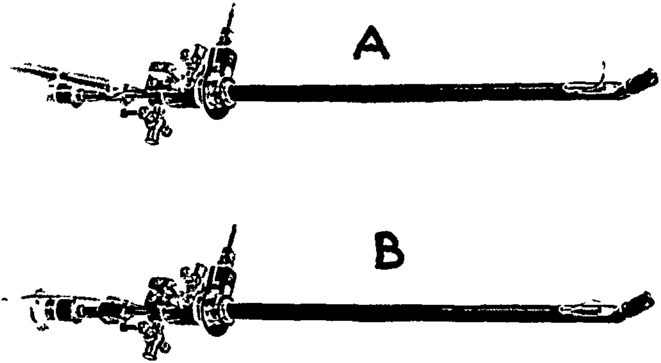

Fig 5 Redewill cystoscope A fulgurating electrode in position B, Blasucci spiral filiform tip ureteral catheter replacing fulgurating electrode, A

Case 5 R F, aged 52, height 5 feet, 11 inches, weight 200, had a hypertrophied prostate grade 1 No residual urine was found, he had had three attacks of epididymitis from a "strain" during the past 18 months He had gonorrhea 15 years ago and again 3 years ago He had posterior urethral strictures necessitating the passage of sounds He refused further treatment and harbored B coli and Proteus in his urine His last attack of epididymitis was March 30, 1949 following what he called a "strain" in the left epididymis He had a chronic low grade infection of the seminal vesicles and ducts Chloromycetin cleared up the attack in 60 hours, whereas in former attacks he had suffered for 16 days He was on the drug 1 week following recovery Two weeks later his urine was sterile

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[25] Crane, J J Epididymo orchitis in industrial surgery J Urol, 34 477–479, 1935

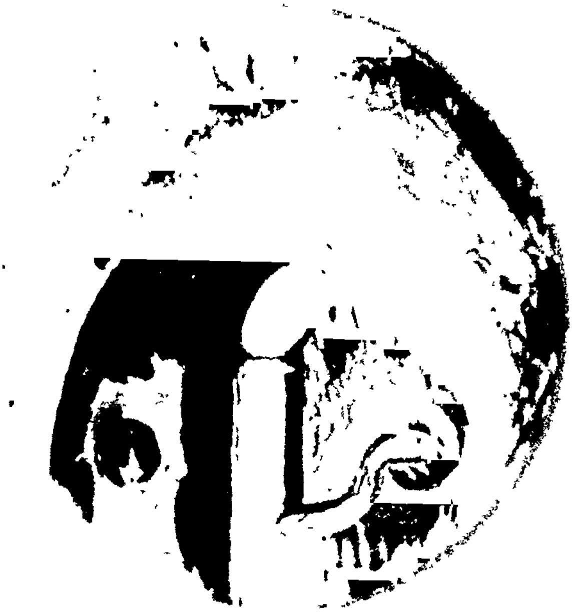

FIG. 6. Depicting Redewill cystoscope in posterior urethra for catheterizing left ejaculatory duct with Blasucci spiral catheter.

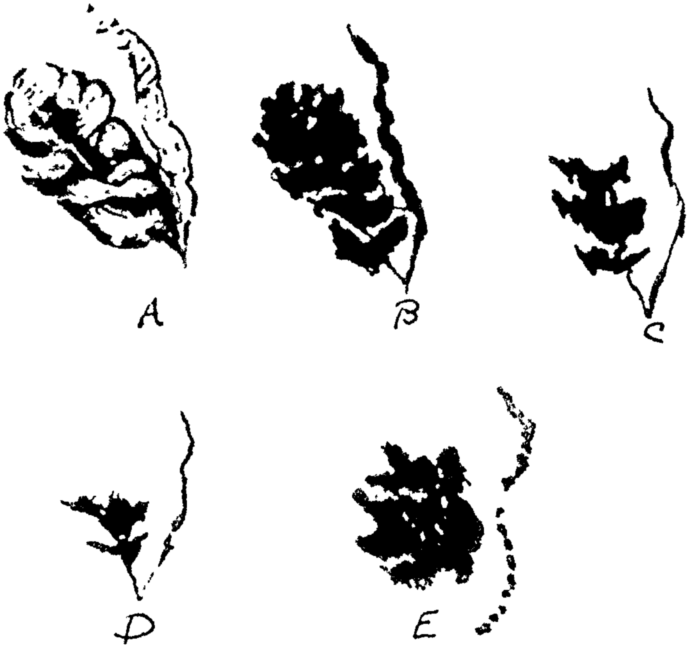

FIG. 7. Sketches of seminal vesicles, normal and infected. *A*, outside contour of seminal vesicles and ampulla. *B*, *C*, *D* and *E*, attempt to inject with diodrast. *B*, injected, normal condition. *C*, improper filling, due to incipient acute infection. *D*, partly filled, due to advanced acute infection. *E*, contour lost, saccular formation due to chronic infection.

COMMENT

With the exception of the attack of mumps described in case 1, which we mention to announce the specificity of Chloromycetin toward that contagious disease, the other 4 cases demonstrate that there is practically always an infection in the genital tract that induces the epididymitis labeled by the patient as a "strain." With the use of penicillin for gram positive infections, and Chloromycetin to clear up all other bacillary infections and with concomitant subsidence of infections of the prostate, ducts and vesicles, we are confident that the true etiological factor producing the so called "strain" epididymitis has been eliminated and therefore, without reinfection, no other such attacks should occur.

Eighteen years ago, before this organization in Minneapolis, I presented a new cystoscope with a retrograde lens,[25] as devised by Wappler for fulgurating papillomata around the vesical neck (fig. 5). The visual field with its telescopic system is very wide, more than 45 degrees. We find that this instrument is adequate for catheterizing the ejaculatory ducts. We adopted another feature that facilitates the catheterizing of the ducts: Instead of using ordinary 4 and 6F ureteral catheters, we use the Blasucci spiral filiform tip ureteral catheters which facilitate entering the ducts. This is accomplished by rotating the catheter from the proximal end when the tip enters the duct. Such a screw tip, when rotated, will follow more readily the tortuous tract of the duct than the straight type (fig. 6).

I believe that in cases of incipient or advanced involvement of the seminal vesicles which cannot be determined by other methods, as many authors reported above have shown, one should catheterize the ducts and inject the seminal vesicles. By using diodrast for the injection of the seminal vesicles, it is possible to detect with fluoroscope and x-ray even slight involvement. We have made sketches showing, *A*, the outside contour of the vesicles; *B*, the contour of healthy injected vessels; *C*, of incipient acute infection; *D*, of advanced acute infection, and *E*, finally of the saccular appearance of seminal vesicles that are chronically infected. This general rule of change of contour (fig. 7) and improper filling may aid urologists in diagnosing pathological conditions in these deep seated, poorly accessible organs.

CONCLUSIONS

Chloromycetin is a new antibiotic that is effective against an impressive range of micro-organisms.

Like streptomycin, Chloromycetin has weak action against gram positive cocci, and in such infections should be supplemented with use of penicillin.

The dose of this drug is discussed and no toxic effects are noted.

The etiological factor producing epididymitis by so called "strain" is infection in the genital tract.

A diagram is presented showing how urine reaches the epididymis.

With the Redewill cystoscope and spiral catheters, more ejaculatory ducts can be catheterized.

Study of injected seminal vesicles will reveal the extent of incipient involvement.

Cases are reported in which acute epididymitis cleared up in a remarkably short time with Chloromycetin.

870 Market St., San Francisco 2, Calif.

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[25] Redewill, F. H.: Urinary bladder tumors diagnosed and treated by new cystosopic methods. Urol. & Cutan. Rev., 36: 145–151, 1932.

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DISCUSSION

DR. RUSSELL D. HERROLD (Chicago, Ill.): Our experience with aureomycin and chloromycetin has been somewhat limited due to the expense of these drugs, about 25 patients. In regard to the gram negative bacilli, they have been utilized chiefly for chronic infections known to be resistant to streptomycin, the sulfa drugs or both. Highly streptomycin resistant bacteria have responded to aureomycin quite satisfactorily. We have noticed, however, that in several instances aureomycin has eradicated the more sensitive bacteria, leaving such resistant species as Pseudomonas or Proteus. Weight for weight, or observations in vitro indicate that streptomycin or dihydrostreptomycin is bactericidal for gram negative bacilli in a higher dilution than either aureomycin or chloromycetin. This perhaps accounts for the favorable response from the administration of one daily injection of streptomycin for infection due to the common gram negative bacilli not associated with other disease.

While bacterial resistance to aureomycin and chloromycetin can develop in vivo, it does not do so rapidly, or to such a great extent as to streptomycin, when bacteriologic cure does not follow therapy. Like other antibacterial agents, failure is likely to occur if infection is associated with other urologic disease.

The flora of uncomplicated, chronic, nonspecific prostatitis, as a rule, are quite highly sensitive in vitro to aureomycin and chloromycetin. Yet, in the few instances where these agents have been used, the results have not been very encouraging. This is comparable to penicillin therapy for chronic prostatitis.

We believe that aureomycin and chloromycetin are two additional drugs of great value but alone are not sufficient to eradicate the more resistant organisms such as Pseudomonas and Proteus. It is here that it might be well to combine one or the other with streptomycin or one of the sulfa drugs, perhaps gantrosan. Combination with penicillin would seem logical in the presence of mixed or resistant coccal infections, for the additive effect, at least, if not synergistic.

I was glad to hear Dr. Carroll's report of a favorable response of Reiter's disease to aureomycin. Recently we have administered chloromycetin to a patient with typical abacterial pyuria. The result was more dramatic than formerly to mepharsen. Very likley, aureomycin would have been equally as effective.

Our technique for in vitro tests of sensitivity differ somewhat from that of Dr. Carroll and his co-workers. We make the inoculations onto solid medium containing the test drug, and titrations are assayed according to the dilution with bactericidal effects.

It was found that E. coli and B. Friedlander were more sensitive to chloromycetin than was A. aerògenes and all more resistant to aureomycin, but within the range of possible therapeutic efficacy to both drugs. Pseudomonas and Proteus were more resistant to both than the above species. Pseudomonas as a rule was more sensitive to aureomycin than chloromycetin. Proteus vulgaris (the more common Proteus) and P. morganii were more sensitive to chloromycetin. However, the one strain of P. mirabilis was more sensitive to aureomycin.

The gram positive groups such as streptococci, staphylococci and diphtheroids were in general more sensitive to aureomycin and chloromycetin than any gram negative bacilli.

The following three methods of choosing an antibacterial agent are in the order of efficacy: 1) direct inoculation of urine, exudate or culture on to media containing various antibiotics; 2) isolation and identification of offending bacteria and the selection of antibiotics known to be most effective for particular species; 3) gram stain of sediment to divide into gram negative bacilli, gram positive cocci, or mixed.

DR. SAMUEL A. VEST (Charlottesville, Va.): Within a very short span of time three new antibiotic agents, chloromycetin, aureomycin and polymyxin, all having comparable antibacterial spectra, have become available for use against infections due to gram-negative organisms. Polymyxin enjoys an advantage over the other two in being the most effective agent currently available against Pseudomonas aeruginosa or Pyocyaneus infections. On the other hand, it has the disadvantage of not being absorbed from the gastro-intestinal tract like streptomycin and requires periodic parenteral injections spaced throughout the day. This mode of administration necessitates hospitalization. Until the advent of these three chemotherapeutic agents we were currently scraping the bottom of the barrel for new and effective antibiotic substances. This was the result of the general development of bacteria resistance to all available chemotherapeutic agents thus making imperative the necessity for the development of new agents with which to attack infections.

The polymyxins are a series of very closely related chemical substances obtained from the growth of a soil bacillus. These compounds are interesting in that they are basically polypeptides with amino acid constituents. According to slight chemical differences these polymyxins are termed, A, B, C, D, E, etc. There are evidently different strains of this bacillus which produces slightly different chemical substances. The antibiotic material extracted from the growth of this bacillus in England was originally known as Aerosporin. It was probably more bactericidal than the Polymyxin B and E, which are the substances reported by Drs. Pulaski and Rosenberg, but the original Aerosporin or Polymyxin A was probably more toxic. In looking over the development of polymyxin one can safely assume that the final substance in this category of drugs has not yet been found, and it is highly probable that the toxic elements will sometime in the future be eliminated. The surgical research unit at Brooke General Hospital affords excellent facilities for clinical and laboratory study of the problems related to surgical infection and continued study by qualified groups such as headed by Major Pulaski is necessary before such drugs can be placed in the hands of the average physician for routine clinical use. This work, therefore, has an excellent background from a standpoint of the character of the work and integrity of the observations.

The results obtained from polymyxin therapy, as reported in this paper, are splendid. Whether this ratio of 10 good results, 7 doubtful and 3 failures will continue to hold over a large series of cases remains to be seen. It is also hoped that bacteria will continue to show a reluctance to the development of resistant strains when the use of this drug becomes more widespread. It is of great interest that polymyxin is ten to one hundred times more effective than streptomycin when used against the rather restricted but susceptible organisms in test tube experimentation.

We have had *polymyxin available for approximately* 12 months in our department but have not used it for two reasons. The first was because of its known toxicity, and the second was that other agents have held priority in our restricted number of cases. At the same time we carried out a number of in vitro sensitivity determinations in urinary tract infection and these in general agree with those of Drs. Pulaski and Rosenberg and other workers with one striking exception. For an example, in 10 cases of gram-negative urinary tract infections 9 were extremely susceptible and sensitive to polymyxin while one was resistant not only to polymyxin but to all other available chemotherapeutic agents both in vitro and in vivo. We were surprised to find, however, in 2 cases, one a nonhemolytic streptococcus, and the second a Beta hemolytic streptococcus, that they were both extremely sensitive to polymyxin. In fact, both were sensitive to .01 mg. per cc.

It is unfortunate that there is evidence of nephrotoxicity and neurotoxicity following polymyxin therapy in man, but it is hoped that these toxic agents may be eliminated from future preparations of the material. Up to the present time these observations have seriously limited its clinical usefulness. It is for this reason that polymyxin cannot be placed in the hands of the average physician for routine use. In early animal experimentation the nephrotoxicity was divided into two separate chemical factions. One produced an antidiuretic effect but this has apparently never been observed in man. The other was a so-called "kidney damaging effect" and it is this that has been observed by Drs. Pulaski and Rosenberg. They mention tubular injury to the kidney, but I would like to ask them how they arrive at the conclusion that the tubule is the point of injury just because the urine shows albumin, red blood cells, white blood cells and a few granular casts. It seems to the writer that such findings indicate a more general injury to the entire nephron beginning at the glomerular membrane.

Another point that this paper raises in question is the development of any products of bacterial metabolism which would inhibit the bacterial activity of polymyxin. Are there such substances produced by resistant strains? From a purely theoretical standpoint, polymyxin should not be the ideal antibiotic in urinary tract infections because studies to date have shown that it is excreted in the urine in an anactive biological form. It is also evident from early experimentation that the effect of this substance is bactericidal in nature and not bacteriostatic. The advent of these drugs brings up the very intriguing possibility of new therapeutic synergism, and it is probable that the combination of various drugs may be more effective in smaller and less toxic doses than is possible with a single agent. I wonder if Dr. Rosenberg has had any experience so far in this field?

The authors have wisely pointed out that polymyxin, like all other agents, is ineffective when there are complicating factors such as obstruction, calculi, etc., in various parts of the urinary tract. We must continue to stress in our teaching that no known antibacterial agent will be affected without the application of well established surgical principles. The availability of so many new drugs makes it imperative that careful bacteriologic studies be done on all urinary tract infections. From a scientific and practical standpoint as well the organisms should be isolated and identified and, if possible, they should be tested both qualitatively and quantitatively as regards sensitivity to these various antibacterial agents.

The writer wishes to thank Drs. Pulaski and Rosenberg and the other authors for their splendid contribution that they are making to a field, which we will find so useful to all of us.

Dr. Henry A. R. Kreutzmann (San Francisco, Calif.): It is somewhat difficult for the average urologist to evaluate the effectiveness of chloromycetin. In the first place, it has been made available for only a very short period of time and, in the second place, the cost of this drug is prohibitive to most patients.

It is usually by grants to investigators, such as Dr. Chittenden and his colleagues, that we are able to obtain definite information on a large series of carefully controlled patients for a sufficient period of time to draw any conclusions.

Many interesting observations are noted in their exceedingly honest report. Their classification of results as: controlled, improved, or unimproved, is an excellent one and should become standard.

Their assertion that almost 75 per cent of the patients showed mixed coccal and bacillary forms and should be treated with multiple antibiotic or chemotherapeutic measures, is of great value.

Dr. Redewill also realizes that a mixed infection may be present and that more than one bacteriostatic agent must be administered simultaneously.

Too often in the past we have been prone to consider the predominant organism as the causative agent and the secondary organisms as contaminants. No doubt, if the methods advocated by both authors are followed, better results will be obtained.

We were greatly interested by Dr. Redewill's explanation on the sudden development of acute epididymitis.

In 1937 we reported the results of simultaneous cutures of bladder urine and excised vasa in 100 patients. Our work showed that no vasal infections were present if the urine cultures were sterile, even though one group was composed of patients with chronic prostatitis.

However, in 20 men who had infected urine and had undergone repeated instrumentation, 40 per cent of the cultures from the vasa were positive.

In another series of patients with infected urine who had never been instrumented, the cultures from either one or the other vasa was positive in 20 per cent of cases.

Our findings were considered positive only in those cases in which the cultures from the bladder and the vasa were identical.

Therefore, in the presence of a bladder infection, there is always the possibility of acute epididymitis developing, either through direct continuity or, as explained by Dr. Redewill, as a result of sudden reflux.

Dr. Chittenden and his associates have used chloromycetin in every conceivable type of urinary infection, while Dr. Redewill has limited his investigations to infections of the epididymis. Their results, however, are comparable. The one factor in which they differ, and in which we also are not too certain, is the daily dosage to be administered and for how long a period of time the drug should be continued.

We have used chloromycetin in a number of patients with cystitis associated with chronic prostatitis. Not only did the bladder become free of infection, but to our great amazement, we found, as did Dr. Redewill, that the prostatic secretion showed only an occasional pus cell. However, it is too soon to say whether these results are permanent.

In one case of acute nonspecific epididymitis the pain and fever disappeared in less than 36 hours, and resolution continued even though only 6 gm. were given over a period of 3 days.

Of all the antibiotics, chloromycetin appears to be the least harmful. We have given patients large doses over long periods of time. For example, one man received 63 gm. in 3 weeks without any ill effects whatsover.

Therefore, we have not hesitated to use this antibiotic in a number of cases of chronic pyelonephritis in children where urological examination showed no gross pathological changes and with good results.

We have administered up to 2 gm. every 24 hours in children, with no ill effects.

These were patients in whom other types of therapy had been tried unsuccessfully.

From our experience, we have learned that the advantages of chloromycetin are: low toxicity, minimal side reactions, and the fact that it can be administered by mouth.

Both of these excellent papers have presented a new antibiotic which, in time, will take its proper place along with our other drugs, and play an important role in combating bacillary urinary infections.

Dr. Clarence G. Bandler (New York, N. Y): I have been enormously impressed by this symposium, and no doubt all of you have been equally enlightened. I will confine my few remarks, however, to the presentation of Dr. Grayson Carroll on the subject of aureomycin.

For some time I have been privileged to conduct some clinical investigations under the aegis of Dr. Walsh McDermott of Cornell University Medical School in New York. I have concentrated my attention upon the utilization of aureomycin in the resistant gram-negative bacillary infections of the urinary tract, especially on E. coli. We have found that aureomycin is singularly useful.

However, not infrequently there is a secondary infection which actually overgrows the original infection, especially is this true of Bacillus proteus. In such cases we are presented with a considerable problem. Aureomycin is absolutely ineffective, we have found, against infections due to B. proteus.

However, combining dihydrostreptomycin with the aureomycin has enabled us to eliminate the dual infection at one and the same time.

A word of warning about aureomycin therapy is advisable. Aureomycin will sterilize the urine of individuals infected with E. coli and some other gram-negative organisms but, after the drug has been discontinued, frequently the original infection will recur, even after sterile cultures have been obtained.

Under these circumstances, we have concluded that it is advisable to continue aureomycin in doses of 250 mg. 4 times a day, for a period of 2 weeks following a week of negative urine cultures.

Despite high concentrations of aureomycin in the blood, recurrences will be observed, and have occurred with a fair degree of regularity.

Relative to the ill effects of aureomycin on the gastro-intestinal tract, I certainly know that it is not pleasant to take and, while it is not essentially toxic, it is certainly disagreeable. Most patients complain of the gastric irritability during the first 48 hours of administration. Nausea and loss of appetite are regularly noted, but these minor symptoms soon disappear.

If, as has been suggested by Dr. Carroll, and no doubt most of you have followed his suggestion, Amphojel or Gelusin are employed as adjuvants, the effect of aureomycin is somewhat diminished.

Several of our patients, one a doctor, and he was the first one to call our attention to this mode of administration, have taken 250 mg. or even 500 mg. (two capsules), of aureomycin submerged in a small amount of white vaseline with a result that no gastric distress has been encountered and the antibiotic has been desirably effective.

The possibilities of chloromycetin being employed as an effective therapeutic agent against gram-negative bacillary urinary infections impresses me very much. However, I am not prepared to report my experiences with this new antibiotic. I believe that it may prove to be an even more effective agent and surely a better tolerated form of medication in the types of infection which have been so admirably discussed by Dr. Grayson Carroll.

DR. FRANCIS H. REDEWILL (San Francisco, Calif.): Gentlemen, you should not sell the combination streptomycin with promizole short. That combination was used by Dr. Lincoln in Bellevue Hospital, New York with remarkable results in acute meningitis. Even at Molokai, Hawaii, the combination has been curing up so many lepers, they are thinking of closing the leper colony. So that speaks very highly for streptomycin and promizole.

DR. IRVING SIMONS (New York, N. Y.): I wish to congratulate Dr. Grayson L. Carroll on having been able to sterilize, even in this small series, 35 of 48 cases of infected urine by means of this new antibiotic, aureomycin.

Some of the investigators said certain things which I did not quite understand; their findings do not agree at all with ours. Having examined at random the urine of 174 patients on the neurological service of about 600 beds at the Goldwater Memorial Hospital, Welfare Island, N. Y. City, quite different figures were reported by our Department of Bacteriology (table 1).

In the first place, in these 174 cases examined, you will notice that there were single infections in 89 and double infections in 33, which was quite the opposite of what was stated as being *found* by one of the investigators; in other words, he found singly *infected urines* in 25 per cent and doubly infected urines in 75 per cent of his series, which incidentally was not very large for statistical purposes.

We found in these very advanced neurologic derelicts, all of which probably had neurogenic bladders, single infections in a *very great* preponderance of the cases, namely, 89 out of 122 cases. And incidentally 52 of the series of 174 cases had sterile urines.

TABLE I. *Incidence of infection in the urine in a series of 174 neurologic cases*

Uninfected cases	52
Single infections:	
B. coli	25
Staphylococcus albus	24
B. proteus	22
Staphylococcus aureus	8
B. diphtheroids	7
B. pyocyaneus	2
Streptococcus (nonhemolytic)	1
Total single infections	89
Double infections:	
B. coli and B. proteus	6
B. coli and Staphylococcus aureus	3
B. coli and Staphylococcus albus	3
B. coli and B. pyocyaneus	1
B. proteus and Staphylococcus albus	4
B. proteus and Staphylococcus aureus	1
B. proteus and B. diphtheroids	2
B. proteus and B. pyocyaneus	1
Staphylococcus albus and Staphylococcus aureus	3
Staphylococcus albus and B. pyocyaneus	2
Staphylococcus albus and streptococcus (nonhemolytic)	1
Staphylococcus albus and B. diphtheroids	1
B. diphtheroids and Staphylococcus aureus	4
B. diphtheroids and micrococcus tetragenus	1
Total double infections:	33
Total infected cases treated	122

You will notice that in the 89 singly infected urines B. coli was found 25, Staphylococcus albus 24 and B. proteus 22 *times (a total of 71 times)*. That, of course, would give a rather gloomy outlook for therapy by antibiotics, as stated by these investigators, as they stated that antibiotics were not very efficacious against gram positive cocci and especially against B. proteus.

Incidentally, these Staphylococcus albus infections were not infections with an occasional coccus, but urines profusely infected with cocci. I think that in many instances investigators catheterize patients and send a little urine to the laboratory and it stands around for a good many hours before the bacteriologist inoculates media with it. We, that is I, because all of this work was done by me personally, inoculate our culture tubes of solid media just after the urine is drawn, so that it arrives at the laboratory already inoculated, and is not allowed to overgrow and give a result which is undependable.

You will notice that 24 cases of Staphylococcus albus were found; these were not just one or two colony infections; they showed 30 or 40 colonies to the drop of urine.

I do not quite understand why the new antibiotics to which we have transferred our interest will not eradicate organisms that we have already been able to eradicate with well known drugs. Mandelamine eradicates B. coli almost as well as it does Staphylococcus albus, which latter, as a rule, is either very quickly eradicated, in about 2½ weeks, or else takes a very long time.

In lantern slide 2, we analyze 36 cases of infected urines which we were able to sterilize by means of mandelamine (not an antibiotic); these results are used merely for comparision and they were most difficult cases, neurogenic bladders, probably the most difficult of all genito-urinary cases to sterilize. Grouped with 32 cases which we could not sterilize, after what we considered to have been treatment a sufficient length of time, we have a series of 68 cases (not counting 32 more cases insufficiently treated, but still under treatment.)

In this series of 36 sterilized cases we were able to eradicate all sorts of organisms, even gram-positive coci and B. proteus, in both of which types of infection the antibiotics are said to have little therapeutic value. I do not want to give the impression that if we are presented with a series of 100 cases of infection with B. coli, the drug mandelamine will eradicate every one of them. But the drug mandelamine will eradicate some of every organism in our bacteriological list, such as B. pyocyaneus, B. coli, and Staphylococcus aureus; and even Staphylococcus albus and B. proteus rather easily.

In regard to the report on the investigation of chloromycetin[1] I read it rather carefully. It is based on the treatment of 50 cases, all of which are abstracted. I was, however, unable to make up my mind whether to discuss it or not, because in many of the cases, in addition to treatment with chloromycetin, several medicinal agents were used, such as streptomycin etc., and even mandelamine.

In our own series we were able to report urinary sterilization in 36 (52.9 per cent by means of mandelamine; 32 were considered failures (47.1 per cent) in the series of 68 cases, thoroughly treated. In addition there are 32 cases still under treatment, which may change the percentages slightly. When we report sterilization ("cure") we merely mean that after sufficient treatment we obtain two negative urinary cultures about 2 or 3 weeks apart. Some of the sterilized cases relapse, if re-cultured once a month for about a year, but some of them do not.

In closing may I say that urinary sterilization by means of mandelamine is a very easy, painless and inexpensive method of therapy. However, in case of failure, we shall be glad to use the newer antibiotics presented here, but not at first.

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[1] The paper on "The Treatment of Bacillary Urinary Infections with Chloromycetin," by Drs. Chittenden, Sharp, Vonder Heide, Bratton, Glazko and Stimpert will be published in November. *Editor.*

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BACTERIAL ENDOCARDITIS FOLLOWING SURGERY, PARTICULARLY SURGERY OF THE URINARY TRACT[1]

EUGENE F. TRAUT AND C. O. MILLER

Endocarditis is an inflammation of the lining of the heart, including the surface of the valves, and often affecting such associated arteries as the aorta, ductus arteriosus and coronaries. The causal organisms can usually be found in the endocardium or the circulating blood. Abacterial forms also occur. The commonest example of endocarditis unaccompanied by a demonstrable blood stream invasion is rheumatic fever.

ETIOLOGY AND PATHOGENESIS

Bacterial endocarditis results from the localization of bacteria on the valves, the lining of the heart or the adjacent vessels. Bacterial invasion of the blood stream is commoner than ordinarily suspected. It is well recognized during pneumonia, furunculosis and gonorrhea, and accounts for metastatic infections in the joints, bones and meninges. Less appreciated are transient bacteremias during acute upper respiratory infections and infections of the urinary tract.[2] Indicating the fairly easy accessibility of bacteria from the environment to the body's tissues is the permeability of the mucous membrane of the gastro-intestinal tract, B. prodigiosus having been recovered from the blood after feeding it with a meal.

Bacterial invasion of the blood followed by endocarditis has been recognized following surgery of infected tissues particularly of the gums or tonsils. Habein and Kretschmer have briefly referred to the possibility of endocarditis after urinary surgery.[3] Streptococci have been isolated from the blood stream in 75 per cent of tooth extractions.[4, 5] Even manipulating an infected tooth may release bacteria into the circulation. I have been able to confirm the presence of bacteria in the blood, usually green or indifferent streptococci subsequent to tooth extraction and after tonsillectomy. Even a fracture or an automobile accident may set off an endocarditis in susceptible individuals.[6] The circulating organisms during acute infections and after surgery vary greatly in cultural characters as well as in virulence.

In acute malignant and necrotizing endocardial inflammation the pneumococcus is most frequently found. Other common invaders are hemolytic streptococci, staphylococci and gonococci. Fungi, including yeasts and actinomyces, have been recovered from the blood and endocardial vegetations. The type of bacteria does not necessarily determine the clinical course nor the severity of the pathological change. Streptococcus viridans has been repeatedly observed as the infecting organism in fulminant endocarditis and Streptococcus hemolyticus has been associated with lingering, subacute cases.[7]

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[1] Read at meeting of Chicago Urological Society January 21, 1948.

[2] Held, I. W. and Lieberson, A.: Pathogenesis of subacute bacterial endocarditis. Am. Heart J., 25: 478, 1943.

[3] Habein, H. C. and Kretschmer, H. L.: *In discussion of prostatic surgery and heart disease* (paper by Kretschmer and Butler). J. A. M. A., 136: 441, 1948.

[4] Okell, C. C. and Elliott, S. S.: Bacteremia and oral sepsis. Lancet, 2: 869, 1935.

[5] Elliott, S. S.: Bacteremia and oral sepsis. Proc. Royal Soc. Med., 32: 747, 1939.

[6] Middleton, W. S. and Burke, M.: Streptococcus viridans endocarditis lenta. Am. J. M. Sci., 198: 301, 1939.

In a small percentage of endocarditides apparently clinically and morphologically identical with the bacterial cases blood cultures are repeatedly sterile. A bacterium of low virulence, Streptococcus viridans, is the organism most commonly isolated from the blood in endocarditis.

Apparently bacteria may lodge on or in a previously normal valve. Such bacteria are usually of the more virulent varieties and produce marked tissue destruction. The mechanism of localization is variously explained. Writers, especially the English, support the existence of preformed capillaries in normal valves of adult hearts. Forbus accepts the concept of capillaries in normal valves and involvement of normal leaflets by bacteria.[8] Probably bacteria can not multiply in the blood stream. The antibody titer in the blood rises and limits the bacteria to fixed tissue.[9] Another immune response is the development of large mononuclear cells in the affected valves. These cells are cytophagic and engulf bacteria, introducing the organisms into the valvular structure. Platelets may accumulate on valve surfaces and form thrombotic deposits, which serve to fix circulating organisms.

Subacute endocarditis always develops in a previously deformed endocardium. The deformity is that most often associated with an inactive or sometimes with even an active rheumatic valvulitis. In late adult life or in the elderly the localizing deformity may be an arteriosclerotic thickening or roughening. In a few the predisposing lesion is the result of luetic mesaortitis. Congenital lesions such as a patent ductus arteriosus, a septal defect or bicuspid aortic or pulmonic valves are predisposing factors more important in youthful subjects. Rheumatic endocarditis may be the underlying lesion even when arteriosclerotic or luetic changes are obvious. A positive serology associated with bacteremia does not always mean that the endocarditis has located on a syphilitic cardiovascular defect.

The cardiac deformities: rheumatic, arteriosclerotic, luetic or congenital, are presumed to act either by mechanically changing the blood flow in such a way as to spray an area of the heart's lining with a stream of bacteria in blood under increased force or the deformities may alter the blood flow in a way to increase the trauma of valvular closure. According to Nedzel, local tissue anoxia is the ultimate cause common to all the influences predisposing to bacterial localization on the endocardium.[10] Previously inflamed valve leaflets have blood vessels which allow bacteria to lodge by embolization.

Associated pathologic changes are either cardiac due to the perforation of valves or the cardiac septa, or to heart failure. Emboli can damage the heart by thrombosing coronary vessels, leading also to abscess of the myocardium or coronary arteritis.

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[7] Kelson, S. R. and White, P. D.: Notes on 250 cases of subacute bacterial (streptococcal) endocarditis studied and treated between 1927 and 1939. Ann. Int. Med., 22: 40, 1945.

[8] Forbus, W. D.: Reaction to Injury. Baltimore: Williams & Wilkins, 1943.

[9] Willius, F. A.: Cardiac clinics 107. Subacute bacterial endocarditis: Pathogenesis. Proc. Staff Meet. Mayo Clinic, 19: 431, 1944.

[10] Nedzel, A. J.: Vascular Spasm, Experimental Studies. Urbana: Univ. of Ill. Press, 1943.

Most embolic phenomena are peripheral. The skin, lung, spleen, brain and kidney are common areas of infarction from emboli.

SYMPTOMS AND FINDINGS

The symptoms of endocarditis are not usually cardiac. They are general and systemic due to the septicemia. Localized symptoms depend upon the location of emboli.

The symptoms of general infection may develop stormily or insidiously. The gradual onset characteristic of endocarditis in the elderly, or people otherwise weakened, is accompanied by periods of low grade fever and chilliness, weakness, inappetence and sweats. Later the spleen is felt. Petechiae may be found especially if the conjunctiva is examined. The fingers and toes may become clubbed. The finger tips are often tender.

A progressive microcytic anemia sets in. Leukocytosis may be moderate or absent. Repeated, careful culturing of the blood may be required to find the causative organism. Blood cultures in bacterial endocarditis are positive in 50 to 75 per cent of cases, depending upon the bacteriological skill employed.

Symptoms of embolization increase with the advance of the disease. There may be chest pain or hemoptysis from emboli in the lungs. Splenic infarcts can cause pain simulating pleurisy on the left side. Gross or, more usually, microscopic hematuria points to infarct in the kidney. Infarcts in the brain may be small, resulting in focal encephalitis or large, producing hemiparesis or meningitis.

Cardiac enlargement, if present, makes the diagnosis of organic heart disease inescapable. Changing heart murmurs are characteristic. Congestive heart failure occurs in a small percentage. Cardiac irregularity, particularly auricular fibrillation, is usually not seen and electrocardiographic studies give negative results in most cases.

DIAGNOSIS

Fever and malaise in a patient with a heart murmur introduce the possibility of endocarditis and indicate the necessity for cultural studies of the blood.

The signs and symptoms of a generalized infection introduce other systemic infections for diagnostic consideration. Endocarditis is mistaken for influenza or pulmonary or miliary tuberculosis, rheumatic fever, brucellosis and typhoid.

The embolic phenomena in the brain lead to diagnoses of meningitis or brain abscess. In the elderly, a hemiplegia resulting from cerebral embolism is mistaken for a cardiovascular accident due to arteriosclerosis or arterial hypertension.

Infarction of the kidney may be called lumbago, renal calculus or urinary tract infection.

Emboli lodging in the lung give rise to symptoms and signs of pleurisy or pneumonia.

Embolization of a coronary artery may be taken to be coronary thrombosis on the basis of atherosclerosis.

PROGNOSIS

Formerly regarded as almost invariably fatal, antibiotic and occasionally chemotherapy can sterilize the blood, resulting in almost certain cure. The outlook depends upon the virulence of the organism, the duration of the process, the extent of the associated pathological changes and the obtaining of competent medical care. Perforation of a valve or septum, other extensive valvular change or necrosis of portions of the brain are, of course, not reversible. Another criterion of possible cure is the susceptibility of the blood-borne bacteria to antibiotic and chemotherapy.

PROPHYLAXIS

Bacterial endocarditis can be avoided by being aware of the susceptibility of individuals stigmatized by rheumatic heart disease, however remote, arteriosclerotic changes in the heart lining, syphilitic aortitis or congenital heart lesions. We must bear in mind the frequent invasion of the blood by bacteria during intercurrent infections of any sort or following any injury, accidental or surgical, of infected tissue.

Use of sulfonamide or penicillin before and after surgery, particularly before and after incision of presumably infected tissue, is a measure of protection for the patient with a heart or aorta stigmatized by rheumatism, arteriosclerosis, lues or a congenital abnormality.

Once a presumptive or even possible diagnosis of active endocarditis has been established or a patient with a heart murmur develops fever, blood should be drawn for culture. Penicillin should be started without waiting for the results of the blood culture. Penicillin must be used in adequate amounts to control the infection as judged by clinical response, sterilization of the blood or according to the susceptibility of isolated bacteria. The treatment must be continued long enough to insure the elimination of the infection. Physicians must be cautioned against stopping treatment too soon.

MATERIAL

Our report concerns 8 patients varying from 42 to 75 years (table 1). One of the patients underwent a hysterectomy for fibromyoma. The other 7 patients were men subjected to surgical procedures for urological diseases. There were 2 transurethral prostatic resections, 1 orchidectomy, 1 urethral stricture dilatation, 1 crushing of a bladder stone in a patient with chronic prostatitis, 1 nephrectomy for pyonephrosis with stone, 1 ureterotomy for nephrolithiasis and cauterization of bladder polyps.

PREOPERATIVE CONDITION

All of the patients walked into the hospital. Three were symptomless. None had fever. Two patients had had angina on effort. One patient each complained of palpitation, irregular heart beat, shortness of breath and swollen ankles. Two gave a history of rheumatic fever and 4 had been told in early life that they had heart leaks. Two had hypertension, 7 had murmurs, 5 of them diastolic and 5 had enlarged hearts. The spleen was not felt in any. All of the 3 having electrocardiographs showed left ventricular strain.

TABLE 1

NAME AND AGE	PAST	PREOPERATIVE		OPERATION	POSTOPERATIVE FINDINGS	CULTURE	TREATMENT	AUTOPSY
		Symptoms	Findings					
E. D. 52	Lues, heart leak	Scrotal tumor	Enlarg. heart, murmur	Orchidectomy	Fever, pallor, mitral and aortic sten., leukocyt.	Strep. viridans	Penicillin 14 mill., sulfa 42 g.	Rheum. H.D., S.B.E.
H. C. 75	Angina	Retent. urine	Enlarg. heart, murmur, 200/80	Transureth. prostat.	Fever, leukocyt.		Penicillin 1.76 mill., sulfa 30 g.	Rheum. H.D., acute bact. endo.
J. H. 47	Heart leak	Uret. colic, hemat.	Enlarg. heart, murmurs	Uret. stone, polyp caut.	Fever, leukocyt.	Strep. viridans	Penicillin 2.96 mill., sulfa 50 g.	Rheum. H.D S.B.E.
O. B. 63	Angina	Retent. dyspnea	Enlarg. heart, murmurs, 200/130	Trans-ureth. prostat.	Fever, pallor, tachycardia, leukocyt.	Staph. aureus	Fluids	Rheum. H.D., acute bact. endo.
J. G. 60	Rheum. murmur	Prostatism	Staph. aureus in urine, murmurs	Lithopaxy	Fever, leukocyt.	Staph.	Sulfa 7 g.	Rheum. H.D., acute bact. endo.
T. F. 60		Flank pain	Mass in r.u.q.	Uret. stone	Fever, delirium		Supportive	Rheum. H.D., acute bact. endo.
C. J. 42	Rheum. G.C.	Dysuria	Enlarg. heart, murmurs, strict.	Sounds, cystost., urethrot., abscess incision	Clubbed fingers, edema	Strep. viridans	Penicillin 290 mill., sulfa 162 g.	Rheum. H.D., S.B.E.
F. L. 47	Heart leak	Metrorr.	Murmurs	Hysterectomy	Fever, lung consolidation, hemoptysis, cyanosis		Penicillin 2.4 mill.	Rheum. H.D., S.B.E.

POSTOPERATIVE CONDITION

Fever and other untoward symptoms appeared in all postoperatively, in 1 case on the third day, in 2 cases on the fourth day, in 2 cases on the fifth day, in 1 case on the seventh day, in one case on the eighth day. The fever was "spiking" in 2 instances. Six cases commenced with chills and sweats. Four became dyspneic. All had tachycardia. Two patients were noted as pale. All (four) of the patients having blood counts had hemoglobin readings below 70 per cent. In the 5 patients with leukocyte counts the leukocytosis exceeded 11,400. The spleen was felt in 1 case. Petechiae were noted in 2 patients. The diagnosis was recognized clinically in only one instance.

Heart failure was present in 1 patient. The only irregularity noted was extrasystoles in 1 patient. None of the patients had joint disease.

In one of the 2 cases not involving hematuria of surgical origin red blood cells were found in the urine.

TREATMENT

None of the patients had had penicillin or sulfa preoperatively. All of the patients had received sulfonamide and penicillin as soon as these drugs had become available.

Five of the 6 patients treated since 1936 received sulfonamide. The total quantities ranged from 42 g., to 55 g. per patient at the rate of 1 g. each 4 hours. In only one instance had the blood level been measured.

The 5 patients treated since 1940 had received penicillin. The total units given each patient were 15.6 mill., 1.8 mill., 30 mill., 2.96 mill. and 288 mill. In only one instance had the susceptibility of the infecting organism been determined.

Three of the patients receiving penicillin obtained fever-free periods interpreted as cures and were discharged from the hospital. The fever recurred in all and was controlled on resumption of the penicillin in larger doses except in only one instrance. In that patient control was apparently obtained in each of two courses of penicillin. Each time the penicillin was stopped at the disappearance of fever. The third bout of fever was uncontrolled by larger doses of penicillin and continued until death.

All patients died from 5 days to 4 months after the surgery. The number of days of survival are 5, 5, 6, 13, 31, 40, 71 and 134. Penicillin and sulfanilamide were used together in 4 patients. The 3 patients with the shortest survival time did not receive penicillin.

PATHOLOGY

Autopsy demonstrated ancient rheumatic valvulitis in each case. In 4 the superimposed endocarditis was of the acute or ulcerative type. In 4 it was subacute, including the 3 cases yielding Streptococcus viridans. In 7 cases the superimposed endocarditis involved both the mitral and aortic valves. One case showed the vegetations on the mitral valve alone.

DISCUSSION

The youngest patient in this group with active endocarditis was 42 years old. Only recently has active endocarditis been allotted its real importance in people of middle life and older.[11] Zeman and Siegal report a woman of 60 years with a ureteral obstruction who died of staphylococcus endocarditis 4 days after cystoscopic examination.[12]

Held and Lieberson refer to the transient bacteremia following cystoscopy.[13]

Creevy presented evidence that water used as irrigating fluid may enter the circulation through open prostatic veins during transurethral resection. Hemolysis of red cells results. He treats the transitory bacteremia resulting from washing bacteria from the prostate into the venous system by giving penicillin and sulfonamide before, during and after resection.[14]

SUMMARY

Seven patients submitting to urological procedures and one to a gynecological operation died of bacterial endocarditis within days or months. All had had rheumatic endocarditis in early life. Their hearts had compensated for the valvular defects and allowed the patients to enter midlife and old age to encounter the diseases incident to later life. Seven of the cases had demonstrable organic heart disease on admission to the hospital, indeed they could be preoperatively recognized as having rheumatic heart disease. None had been given sulfonamide or penicillin preoperatively.

In only 1 of the 8 patients was the postoperative bacterial endocarditis recognized.

Blood cultures in 5 patients yielded Streptococcus viridans in 3, Staphylococcus aureus in 2. Five patients received sulfonamide; 5, penicillin; 4, penicillin combined with sulfonamide; and 1, sulfonamide alone.

In 3 patients treated with penicillin the unrecognized endocarditis had apparently been controlled but treatment had been stopped prematurely. Subsequent efforts to control the infection proved unsuccessful. All died. Autopsy disclosed bacterial endocarditis in all.

CASE REPORTS

Case 1. E. D., a man aged 52, walked into the hospital because of a scrotal tumor. He had an enlarged heart with a loud systolic murmur. A testicular tumor was removed. The pathological report was chronic epididymitis. Nine days later the patient had chills, sweats, and fever. The cause of the fever was unknown; it disappeared under penicillin and sulfonamide. The patient returned 3 weeks later with fever, which 14 million units of penicillin did not control. Endocarditis was unrecognized clinically. Autopsy showed subacute bacterial endocarditis engrafted on old rheumatic endocarditis of the mitral and aortic valves.

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[11] Traut, E. F., Carter, J. B. and Gumbiner, S.: Endocarditis in the elderly. To be published in geriatrics. Also Trant, E. F., Carter, J. B. and Zumbiner, S.: Clinical aspects of endocarditis in the elderly. To be published in Postgraduate Medicine.

[12] Zeman, F. D. and Siegal, S.: Acute bacterial endocarditis in the aged. Am. Heart J., 29: 597, 1945.

[13] Held, I. W. and Lieberson, A.: Pathogenesis of subacute bacterial endocarditis. Am. Heart J., 25: 478, 1943.

[14] Creevy, C. D.: Hemolytic reactions during transurethral prostatic resection. J. Urol., 58: 125, 1947.

Case 2. C. H., a man of 75, walked into the hospital with urinary retention and a history of angina on exertion. He had hypertension, an enlarged heart and a systolic murmur at the apex. A transurethral prostatic resection was done. Nine days later he had fever and a diastolic murmur. Penicillin and sulfonamide for 11 days controlled the fever. He was admitted to the hospital 9 days later with a spiking fever. Sulfonamide and penicillin did not control the unrecognized endocarditis. No blood culture was made. Autopsy showed acute bacterial endocarditis of mitral and aortic cusps, and ancient rheumatic valvulitis.

Case 3. A woman of 47 walked into the hospital because of menorrhagia. A systolic and diastolic murmur had been recognized years before. Hysterectomy, bilateral oophorectomy, salpingectomy and appendectomy were done. Three days later fever, dyspnea and hemoptysis developed. No blood culture was made. Penicillin had no effect. Endocarditis was unrecognized. Autopsy showed vegetative endocarditis engrafted on old rheumatism of the mitral and aortic valves.

Case 4. J. H., a man of 61, walked into the hospital because of renal colic. His heart was found to be enlarged. He had systolic and diastolic murmurs. A stone was removed from the ureter. A bladder polyp was cauterized twice. Seven days later fever, systolic and diastolic murmurs and petechiae developed. Sulfanilamide controlled the fever. The patient was readmitted 1 week later with fever, leukocytosis and anemia. Penicillin for 5 days dispelled the fever. He was discharged after 2 weeks. He was readmitted 2 weeks later. Streptococcus viridans was isolated from the blood. Penicillin and sulfonamide were of no benefit. Autopsy showed subacute endocarditis engrafted on healed aortic rheumatic valvulitis.

Case 5. O. B., a man aged 63, walked into the hospital with acute urinary retention, angina and dyspnea on exertion for 16 years. The temperature was 98.6, pulse 72. The heart was enlarged to the left; systolic thrill and systolic and diastolic murmurs were present over the aortic area. The temperature was 101.4 F on the day that transurethral prostatic resection was done. The patient had a chill and a temperature of 105 F later. Staphylococcus aureus was isolated from the blood. Autopsy showed ulcerative endocarditis engrafted on calcific aortic stenosis.

Case 6. J. G., a man of 60, walked into the hospital with prostatic obstruction. He had had rheumatic fever in childhood and a systolic murmur for 43 years. The heart was not enlarged. Staphylococcus aureus was found in the urine. Fever, chills and petechiae developed 4 days after lithopaxy. Staphylococci were isolated from blood. Sulfa was without benefit. Autopsy showed acute bacterial endocarditis engrafted on chronic rheumatic valvulitis.

Case 7. T. F., a man of 60 years, walked into the hospital with pain in the flank. A large kidney was felt. No heart abnormalities were detected. A pyonephrotic kidney with calculi was removed. Fever, chills and delirium developed 4 days later. Autopsy showed ulcerative endocarditis engrafted on ancient rheumatism of aortic and mitral valves.

Case 8. C. J., a Negro aged 42, walked into the hospital with retention of urine. He gave a history of rheumatic fever and gonorrhea. The heart was enlarged. A diastolic murmur was present. Chills and continuous fever developed 8 days after catheterization. Penicillin and sulfonamide were given. He was discharged with a diagnosis of tuberculosis. The diagnosis was changed to endocarditis 97 days after onset when clubbed fingers, systolic and diastolic murmurs and hematuria were found. Blood culture yielded Streptococcus viridans. The bacteremia was uncontrolled by 288 million units of penicillin and 162 g. of sulfonamide. Autopsy showed vegetative endocarditis engrafted on old rheumatic mitral and aortic valvulitis.

CONCLUSIONS

Patients with a history of rheumatic fever or with findings of rheumatic, arteriosclerotic or luetic deformities of the endocardium or aorta or with congenital anomalies are to be regarded as poor surgical risks. Any surgery involving manipulation of infected tissue is to be preceded and followed by penicillin and sulfonamide. Signs of infection in such patients following operation should suggest the likelihood of bacterial endocarditis. Such infections are to be treated adequately as presumptive infections of the endocardium.

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BLOOD VOLUME DETERMINATIONS IN THE UROLOGICAL PATIENT: AN ADJUNCT IN PREOPERATIVE AND POSTOPERATIVE MANAGEMENT[1]

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The purpose of this discussion is to present our experiences with blood volume determinations as an aid to the management of the urological patient. This study was initiated with the hope of minimizing complications during and following surgery in patients ordinarily considered poor surgical risks and showing varying degrees of debilitation, weight loss, cardiorespiratory disease, or advanced age. Our observations are based on 53 blood volume determinations in 40 such patients.

The circulating blood volume may be defined as the sum total of the plasma and the available red cell mass. While these determinations have been employed for several decades by physiologists, it is only recently that a method sufficiently accurate for general employment has been popularized. The Evans blue dye technique, developed mainly by Gregersen, has made possible the performance of these determinations in any well-equipped hospital. The method consists of the electro-colorimetric measurement of the intensity of the dye, T-1824, ten minutes after it is injected intravenously into the patient, and comparing it with a known standard. The technique can be mastered by any competent laboratory technician.

The studies of Lyons, Clarke et al., and others have emphasized the severe blood volume deficits existent in individuals chronically ill with cancer, infection, and other debilitating disease. With advanced age the relationship to the urological patient becomes obvious. The chronically ill patient with blood volume deficit withstands surgical procedures poorly in a manner similar to the individual who has undergone blood volume depletion as a result of wounds or trauma; both constitute excellent candidates for shock and delayed convalescence.

RESULTS

The 53 blood volume determinations carried out on the 40 patients of this series were performed between April 1 and July 18, 1948. Since patients included in this series, in the majority, were selected because, clinically, they appeared as poor surgical risks, a review of the type of case is indicated.

The age distribution is shown in table 1. The youngest patient was 18 and the oldest 95; the average age was 62.5 years.

Associated disease conditions are shown in table 2. The predominant groups are those frequently encountered with the changes of senility.

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[1] Read at annual meeting of South Central Section, American Urological Association, St. Louis, Mo., October 26, 1948.

The presenting urological condition of these patients is shown in table 3. Thirty of the cases were clinically diagnosed as benign prostatic *hypertrophy*; 3, prostatic carcinoma with metastases; 3, carcinoma of the bladder; 1, polycystic kidney disease; 1, bacteremia with a left perinephric abscess and pelvic abscess secondary to an undiagnosed ruptured appendix; 1, renal tuberculosis; and, 1, horseshoe kidney with bilateral hydronephrosis and clinical anemia.

TABLE 1. *Age distribution*

AGE	NO. CASES
10–19	1
20–29	2
30–39	2
40–49	—
50–59	10
60–69	11
70–79	10
80–89	3
90–99	1

TABLE 2. *Associated diseases*

1. Arteriosclerosis, severe		21
a. Hypertensive heart disease with cardiac insufficiency	9	
b. Cardiac and or allergic asthma	3	
c. Chronic auricular fibrillation	2	
2. Cerebral vascular accident		2
3. Syphilis		3
a. Neurosyphilis with optic atrophy	1	
b. Tabes	1	
c. Aneurysm	1	
4. Pulmonary		3
a. Bronchitis with bronchiectasis	1	
b. Emphysema, severe	1	
c. Emphysema, severe with spontaneous pneumothorax	1	
5. Others:		
a. Cervical fracture with Brown-Sequard syndrome	1	
b. Parkinsonianism	3	
c. Diabetes	2	
d. Hypothyroidism	1	
e. Duodenal ulcer	1	
f. Bacteremia, with pelvic and perinephric abscess	1	

Weight loss is likewise shown in table 3. The 30 patients with benign prostatic hypertrophy lost on an average 15.4 pounds; the range was 0 to 60 pounds. The 3 patients with prostatic carcinoma and metastases averaged 45.3 pounds loss. The three patients with carcinoma of the bladder (Broders' grade 2 and 3) averaged 27.6 pounds loss. The one patient with bacteremia and perinephric and pelvic abscesses showed a decline in weight over a 4 month period from 122 pounds to 82 pounds. The case of polycystic disease, with severe hypertension and mild azotemia, showed a weight loss of 10 pounds. Weight variations constitute the basis for blood volume deficit calculations. The weight prior to the onset of illness is accepted as the patient's normal except in instances of marked obesity or asthenia where standard tables for age, height and weight are used.

The average blood volume deficit in the patients with benign prostatic hypertrophy was 1263 cc., or 18 per cent of the normal blood volume. The spread was from a normal blood volume in five instances to a deficit of 3790 cc or 47 per cent—the lowest in the series (table 3). The average blood volume deficit for the 3 cases of prostatic carcinoma was 1933 cc or 31 per cent deficit; the 1 case of polycystic disease was interesting from the standpoint that there was a 3000 cc or 34 per cent blood volume deficit. The deficit for cases of bladder carcinoma is not valid because these patients had been losing blood, and, in all instances, replacement therapy was being given.

Weight loss was not constantly indicative of the blood volume deficit. There were eight (20 per cent) patients with abnormal blood volume deficits, averaging 30 per cent, who apparently had lost no weight. On the other hand, a very small weight loss may be associated with a large blood volume deficit. For example, the patient with polycystic disease showed a 10 pound weight loss with a calculated blood deficit of 3000 cc. In only 1 case in the series was weight loss noted and no blood volume deficit found. Diminution in blood volume was usually associated with weight loss.

TABLE 3. *Diagnosis, weight and blood volume variations*

TYPE OF CASE	NO. OF CASES	WEIGHT LOSS RANGE	AVERAGE WEIGHT LOSS	BLOOD DEFICIT RANGE	AVERAGE BLOOD VOLUME DEFICIT
		lbs.	*lbs.*		
Benign prostatic hypertrophy	30	0–60	15.4	0 cc to 3790 cc	1263 cc (18%)
Prostatic carcinoma with Metastases	3	35–55	45.3	1300 cc to 2750 cc	1933 cc (31%)
Carcinoma of bladder	3	7–46	27.6	500 cc to 1400 cc	900 cc (17%)
Polycystic kidney disease	1	10	10	—	3000 cc (34%)
Miscellaneous	3	4–40	16	650 cc to 1740 cc	1313 cc (20%)

There was no constant relationship between the blood volume and red blood cell counts, hematocrit, and hemoglobin determinations, the customary laboratory procedures employed in determining the status of the urological patient prior to surgery. This constitutes a striking revelation and is illustrated by the data on the following case: A well-developed, well-nourished white man, aged 66, on whom a suprapubic prostatectomy was subsequently performed showed the following laboratory findings: hemoblogin, 16.5; hematocrit, 46; red blood cells 5,200,000; plasma proteins, 7.7 gm.; blood urea nitrogen, 13 mg./0/0. The patient had a blood volume of only 69 per cent of his expected normal.

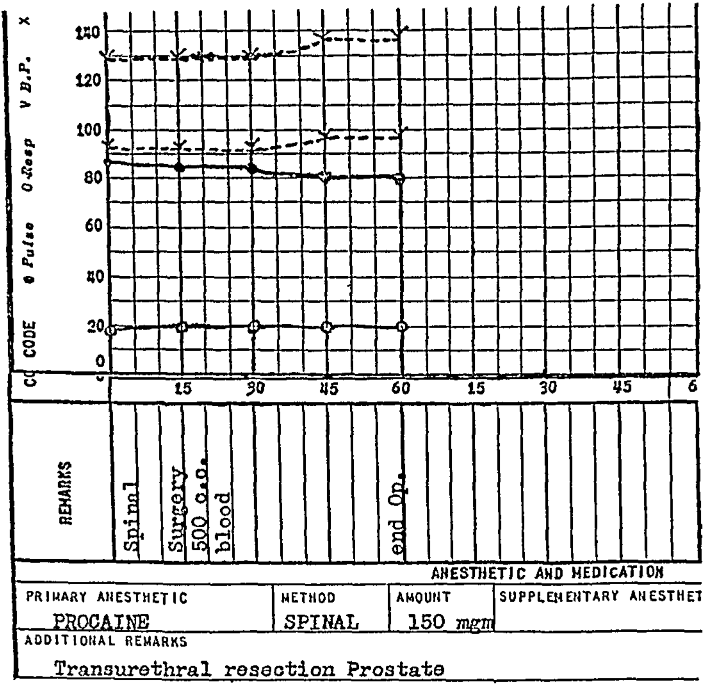
High normal hematocrit still may mask a blood volume of 75 per cent or less. In these cases there were 22 per cent with a hematocrit less than 40; yet 75 per cent of all patients studied had blood volumes 70 per cent or less. Of the 22 per cent with a hematocrit lower than 40, one-third had blood volumes above 90 per cent. In 78 per cent of the initial examinations the hematocrit was above 40 (range 41 to 55) and the actual blood volume varied from 60 to 100 per cent of normal.

In the 36 operative procedures performed on these 40 patients, spinal anesthesia with procaine or pontocaine was used on 31 cases, caudal in 2, ether inhalation in 2, and sodium pentothal in 1 case. In only 2 instances did the blood pressure drop or pulse rate rise appreciably, both while the patients were under spinal anesthesia. One patient was a 35 year old man with a calculated 2000 cc (26 per cent) blood volume deficit who had not had replacement therapy. The other patient was a 73 year old man undergoing retropubic prostatectomy. The blood pressure fell when the Trendelenburg position was assumed, though the pulse rate remained unchanged; the blood pressure returned to normal after 100 cc whole blood was infused and remained normal throughout the remainder of surgery.

TABLE 4. *Operative procedures*

TYPE OF SURGERY	NO. OF CASES	COMPLICATIONS (POST-OP)
Transurethral resection	23	1 death; 3 postoperative hemorrhages on 6th, 14th and 20th days
Retropubic prostatectomy	3	None
Bilateral orchiectomy	2	None
Suprapubic cystostomy with implantation of radon	1	Died on 23d p.o. day (cardiac failure)
2-stage suprapubic prostatectomy	1	None
1-stage suprapubic prostatectomy	1	None
Bilateral nephroplasty and *sympathectomy*	1	None
Cystectomy (total) with cutaneous ureterostomy	1	None
Pyeloplasty-heminephrectomy and nephropexy	1	None
Nephrectomy and injury to inf. vena cava	1	None
Drainage, perinephric abscess and pelvic abscess (postappendiceal)	1	Pelvic abscess requiring further drainage

The other 34 operative procedures were performed on patients who had calculated adequate blood replacement. In these, the operative course was smooth and uncomplicated with one exception. A 95 year old arteriosclerotic, hypertensive patient was given 2000 cc of whole blood over and above his calculated blood volume deficit preoperatively. Under spinal anesthesia a transurethral prostatic resection was done, with blood transfusion begun early in surgery. The surgical procedure was completed without difficulty. However, on returning to the ward the systolic blood pressure rose to over 300 mm. Hg., and profuse hemorrhage ensued. Suprapubic cystostomy with packing of the prostatic fossa was necessary. Anuria and uremia followed and death occurred on the fourth postoperative day. It is conceivable that transfusions in excess of the calculated normal blood volume may have resulted in this unsatisfactory termination.



ANESTHETIC AND MEDICATION

PRIMARY ANESTHETIC	METHOD	AMOUNT	SUPPLEMENTARY ANESTHET
PROCAINE	SPINAL	150 mgm	

ADDITIONAL REMARKS

Transurethral resection Prostate

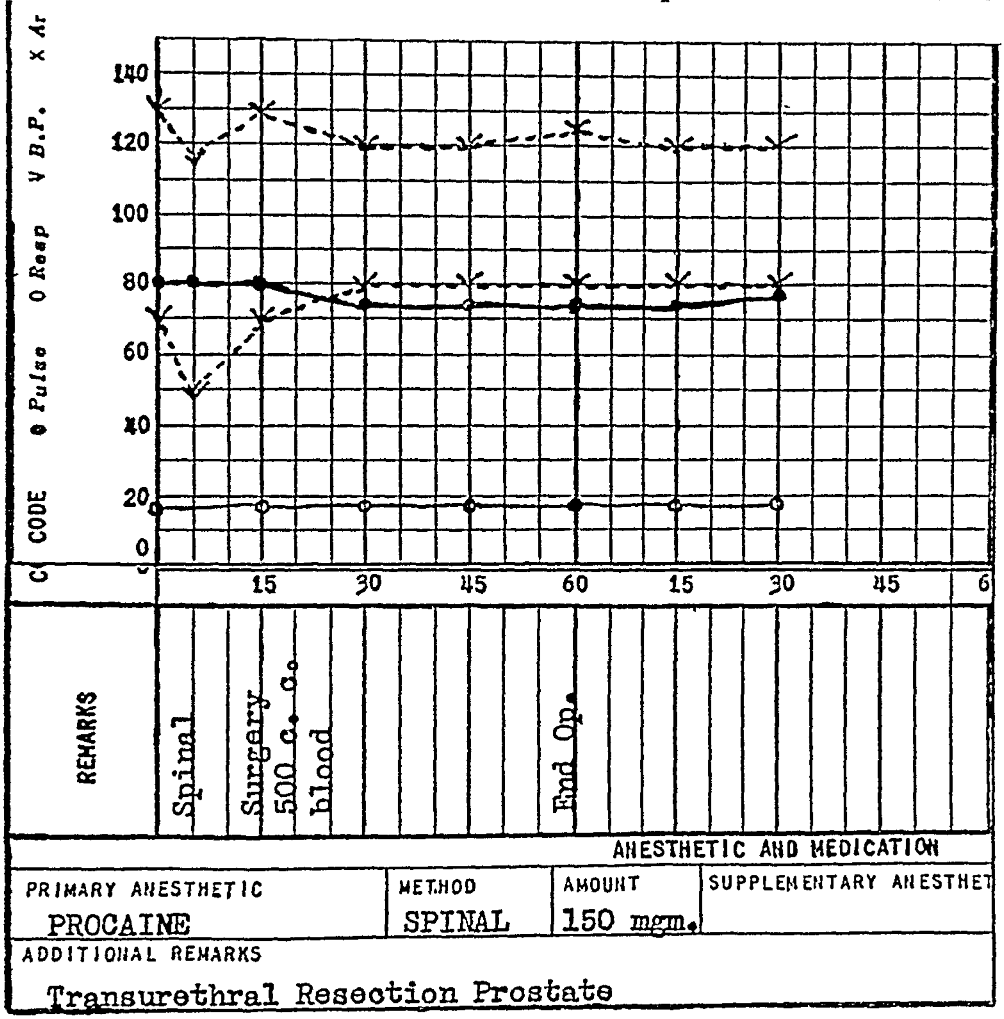
FIG. 1. Case 8. White man aged 63; fracture of C-6 and 7 with Brown-Sequard syndrome; 30 pounds' weight loss. Replacement 1100 cc.

Delayed complications (table 4) included three postoperative hemorrhages, occurring on the sixth, fourteenth, and twentieth days after transurethral resection. Of these, that on the twentieth postoperative day, occurring in a 60 year old, blind white man with neurosyphilis and hypertension, was severe, the patient returning to the hospital in mild shock. One patient, a 74 year old man, died on the twenty-third postoperative day following suprapubic implantation of radon for grade III bladder carcinoma. He had hypertensive heart disease, and death was attributed to cardiac failure.

TYPICAL CASES

With the exception of the 2 cases previously mentioned, one with a calculated deficit of 2000 cc without replacement and the 95 year old patient with over-replacement, the operative course in all instances was remarkable smooth. The following brief case summaries are considered typical:

Case 8. A 65 year old white man sustained a compression fracture of C 6 and C 7 with resultant Brown-Sequard syndrome. While undergoing treatment for this injury, obstructive symptoms of prostatism developed, necessitating prostatic resection. This patient had lost 30 pounds' weight during hospitalization of approximately 3 months. The blood volume determination revealed a shortage of 1100 cc (20 per cent), which was corrected. Transurethral resection was performed under spinal anesthesia. The blood pressure and pulse remained constant throughout the procedure. Five hundred cubic centimeters of blood were given



ANESTHETIC AND MEDICATION

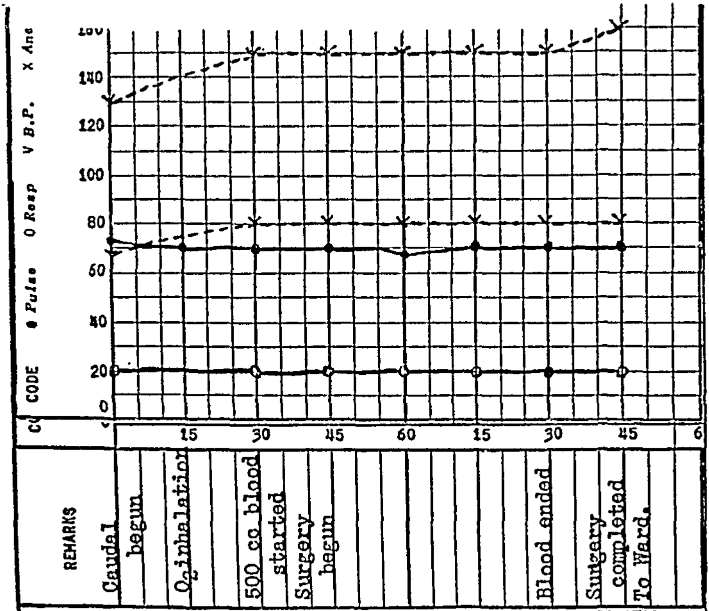
PRIMARY ANESTHETIC PROCAINE	METHOD SPINAL	AMOUNT 150 mgm.	SUPPLEMENTARY ANESTHET

ADDITIONAL REMARKS
Transurethral Resection Prostate

FIG. 2. Case 28. White man aged 54; severe parkinsonism; bedfast for 1 year; arteriosclerotic heart disease with congestive failure. Initial blood volume 53 per cent of expected normal; replacement 4000 cc.

in the operating room. Figure 1 illustrates the anesthetic record. Convalescence was uneventful.

Figure 2 illustrates the anesthetic record of a patient (case 28) classed as chronic shock who had adequate replacement therapy. This 54 year old white man had diagnoses of 1) paralysis agitans, moderately severe; 2) arteriosclerotic heart disease with congestive heart failure; 3) benign prostatic hypertrophy with obstruction. He had been bed-fast for approximately 1 year and was nearly completely helpless, showed dyspnea, ankle edema, marked pallor, and a 20 pound weight loss. Blood volume determination revealed a deficit of 3800 cc (47 per cent), the lowest in this series. After 1700 cc replacement, the ankle edema, dyspnea, and pallor disappeared. Thereafter, the patient fed himself, and became ambulatory. After complete replacement, a transurethral resection was done under spinal anesthesia with the blood pressure and pulse rate remain-



ANESTHETIC AND MEDICATION

PRIMARY ANESTHETIC	METHOD	AMOUNT	SUPPLEMENTARY ANESTHET
PROCAINE	CAUDAL		

ADDITIONAL REMARKS

Transurethral Prostatectomy; orchiectomy

FIG. 3. Case 31. White man aged 78; prostatic carcinoma with generalized metastases urinary obstruction; cardiac failure. Replacement 1700 cc.

ing near 120/80 and 84, respectively, throughout. Convalescence was uneventful except that voiding was unsatisfactory and a further resection was necessary. This operative procedure was likewise smooth. Thereafter the patient voided freely, carried no residual, and was ambulatory on discharge.

The anesthetic record of case 31 is shown in figure 3. This 78 year old white man had adenocarcinoma of the prostate with metastases, also marked arteriosclerosis with congestive heart failure treated by digitalization. He had lost 35 pounds' weight. Hematocrit was 44 and plasma proteins 7.7 gm. per cent. The calculated blood volume deficit was 1700 cc or −29 per cent. The Anesthesia Department is on record that this patient was an extremely poor anesthetic risk; however, transurethral resection and bilateral orchiectomy were performed without the blood pressure falling below 130/66 or the pulse exceeding 72. Convalescence was normal and patient was discharged ambulatory on the fourteenth postoperative day.

POSTOPERATIVE OBSERVATIONS

The majority of the patients who have had adequate replacement therapy recovered uneventfully following surgery. Weight loss was nil or minimal and those with preoperative weight loss showed weight gains. Strength and appetite were maintained or accentuated.

Several blood volume studies in the series were made only on postoperative patients because convalescence was proceeding slowly. A typical case was the 81 year old white man who had undergone a suprapubic prostatectomy 35 days prior to the blood volume determination (case 17). The suprapubic tube had been removed but the cystostomy failed to heal. The blood volume determination disclosed a 1000 cc (16 per cent) shortage. Replacement therapy was completed in 1 day. The next day the suprapubic wound remained dry; 5 days later the wound was completely healed. This, certainly, may have been purely coincidental.

DISCUSSION

The technical improvements in urological surgery in the last two decades and associated progress in the development and use of antibiotics, and understanding of the mechanism of fluid and electrolyte balance have markedly lowered mortality figures, particularly in the aged patient; yet further advances in this field are to be made, principally in the realm of preoperative and postoperative care. Clinical observations in this series of patients suggest that blood volume studies and blood replacement offer a further safeguard in the management of the urological patient. Specific effects of adequate blood replacement, other than the documented lack of untoward reactions during surgery, remain largely those of gratifying clinical impressions of uneventful and rapid convalescence.

Lyons has described a condition termed "chronic shock," which, though controversy over the use of the term may arise, appears to be proved as a definite clinical entity. This chronic debilitative state implies protein depletion in tissue and whole blood but not necessarily a decrease in the concentration of blood proteins or hemoglobin. Because these proteins, and especially hemoglobin, are often maintained at the sacrifice of all other protein elements and may be the last element to fall, clinical recognition of the low blood protein reserve may not be evident from the hematocrit, hemoglobin, red blood cell count, and plasma protein determinations.

The correlation of blood volume with body weight has been shown by Mather to be as satisfactory as that with height or surface area. It has been shown that an acute loss of 30 to 40 per cent of the circulating blood volume of a normal man is followed in 1 to 2 hours by the characteristic symptoms of shock. Spinal anesthesia, a small amount of blood loss at surgery, trauma, etc., can throw these patients from the susceptible to the actual state of shock.

Seeley emphasizes the general lack of appreciation of the disparity between circulating volume and the capacity of the vascular tree under conditions of trauma, hemorrhage, and anesthesia. He further stresses the danger of the use of plasma alone where there is a deficiency in the total circulating red cell mass, the usual finding in patients of the type reported. Even the relatively normal patient is subject to circulating blood volume variations in response to certain anesthetic agents. Spicer and Pulaski, in a study of 25 normal patients before and after anesthesia, observed that with spinal anesthesia, there is an average drop in the circulating blood volume of 14 per cent; that there is no appreciable drop under ether anesthesia. Older, debilitated patients can well be expected to react more drastically than those normal patients studied.

Lyons and Clark observed that the restoration of blood volume precedes significant recovery of weight during recovery from debilitating illness. The wounds of anemic patients heal slowly and convalescence is generally retarded. The anemic patient is more susceptible to and recovers more slowly from infection. The time required for red blood cells, plasma and tissue protein replacement by natural processes may fail to meet the surgical exigency.

In this series the correction of blood volume deficit by whole blood transfusions is considered to be the most important single factor in the preparation of these patients for surgery, and their very satisfactory postoperative course. It appears, as stated by Spicer, that, "the advantage of adequate replacement therapy after blood volume determination will become more evident in the future by the reduced incidence of operative shock, postoperative wound dehiscence, infection, and poor wound healing."

SUMMARY

Blood volume studies in 40 urological patients are presented.

The Evans blue dye method of blood volume determination has proved to be a clinically reliable index of total circulating blood volume in the patient with weight loss and/or chronic debilitating disease, simple enough to be employed in the average hospital.

Thirty-five operative procedures are reported in which adequate replacement of blood volume deficit was accomplished preoperatively with gratifying results. These patients appear to tolerate surgery better, and convalescence appears hastened.

Preoperative blood replacement in the patient undergoing major urological surgery has been a most important contribution to the operative and postoperative course of the patients presented in this series.

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CLINICAL EVALUATION OF A BACTERICIDAL DETERGENT FOR HAND PREPARATION IN UROLOGIC PRACTICE[1]

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During the last few years considerable interest has developed concerning the clinical application of the newer cleansing agents. These include some of the so-called detergents and also a bactericidal agent most commonly referred to as G-11 and officially designated as hexachlorophene. Utilizing a biological, in vivo technique we found that a three minute wash with soap, containing 2 per cent hexachlorophene was superior to the routine 10 minute surgical scrub[2]. Such a 3 minute brushless cleansing eliminates much of the time and all of the skin irritation that are incident to repeated surgical scrubs. In urologic practice where repeated hand cleansing is necessary, any improvement in technique which safely eliminates the brush is obviously worthwhile. As a sequel to our original evaluation of detergents and hexachlorophene as substitutes for the routine scrub, we have, in the urology clinic, carried out further studies on the practical use of the detergent, pHisoderm, containing 3 per cent hexachlorophene.

Several reports concerning the effect of hexachlorophene on the skin flora have appeared.[3, 4, 5, 6] All of these studies have utilized the colony count method of evaluation. That is, colony counts on hand rinsings obtained before and after, or during cleansing have been made and these presented as an indication of cleansing effect. The colony count method, however, does not designate the pathogenic from the nonpathogenic bacteria nor does it obviate the ever present problem of bacteriostatic as against bactericidal effect.

In an investigation previously reported[2], we utilized a biological technique in which the hand rinsings were injected intraperitoneally into mice and the resultant death rate used as a basis for evaluation. The inherent resistance of mice to bacterial infection is well known, and in order to decrease the animal's resistance and to make the pathogenic effect of hand rinsings manifest, the hand rinsings were injected along with gastric mucin.[7] This substance reduces the animal's resistance about one million fold. As a consequence the least pathogenic bacteria is lethal to the injected animal; whereas saphrophytes remain innocuous to the mice even when injected with mucin.

Utilizing the animal injection technique, we made a comparison of the killing effect of hand rinsings obtained after a 10 minute surgical scrub with those obtained after a 3 minute brushless wash with soap containing 2 per cent hexachlorophene.[3] These rinsings were obtained on 5 consecutive days from subjects

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TABLE 1.—*Intraperitoneal injection, with mucin, of peptone rinsings taken after cleansing*

HEXACHLOROPHENE (36 CLEANSINGS)		ROUTINE SURGICAL SCRUB (42 SCRUBS)	
No. of mice injected	Dead	No. of mice injected	Dead
348	28	445	56
Mortality 8.0%		Mortality 12.5%	

P—less than 4%.

TABLE 2.—*Intraperitoneal injection, with mucin, of peptone rinsings taken after cleansing. Contamination with 5 ml. of hemolytic streptococcus culture on first day of series*

	HEXACHLOROPHENE 3 MINUTE WASH (6 SUBJECTS)			ROUTINE SURGICAL SCRUB 10 MINUTES (7 SUBJECTS)		
	No. of mice injected	Dead	Per cent	No. of mice injected	Dead	Per cent
First day	60	59	98.5	70	69	97
Second day	60	7	11.7	70	27	38.6
Third day	60	9	15	70	32	45.7
Fourth day	60	5	10	70	9	15
Fifth day	60	8	16	70	13	21.7

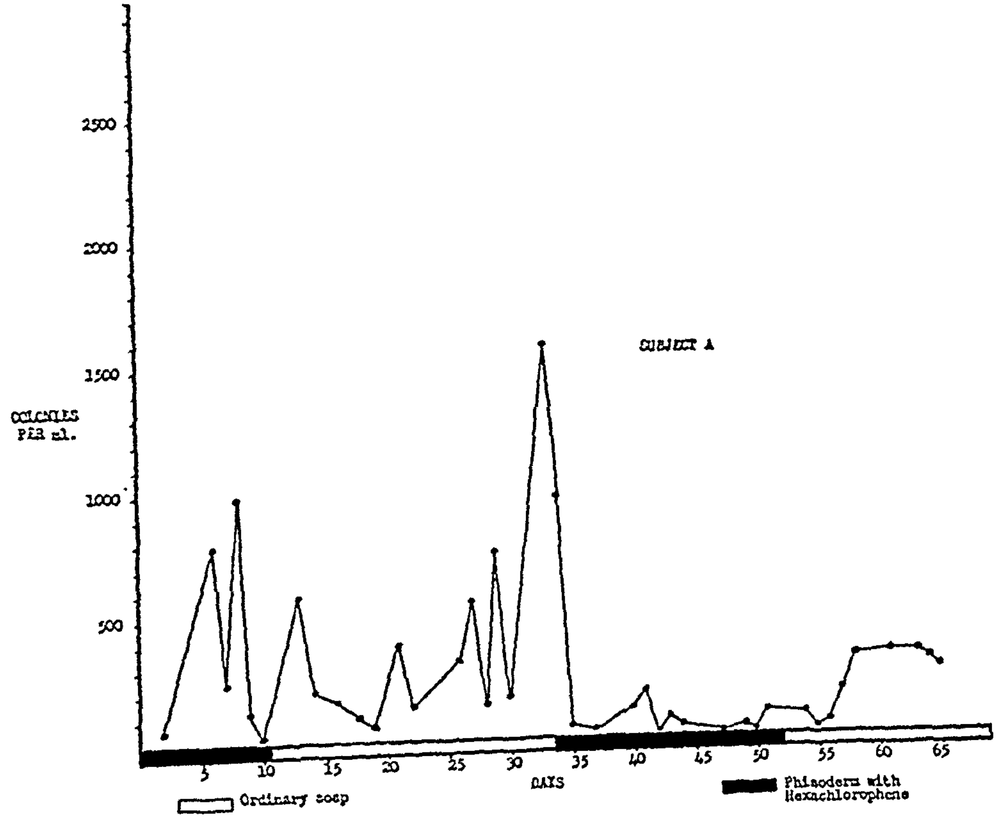

FIG. 1

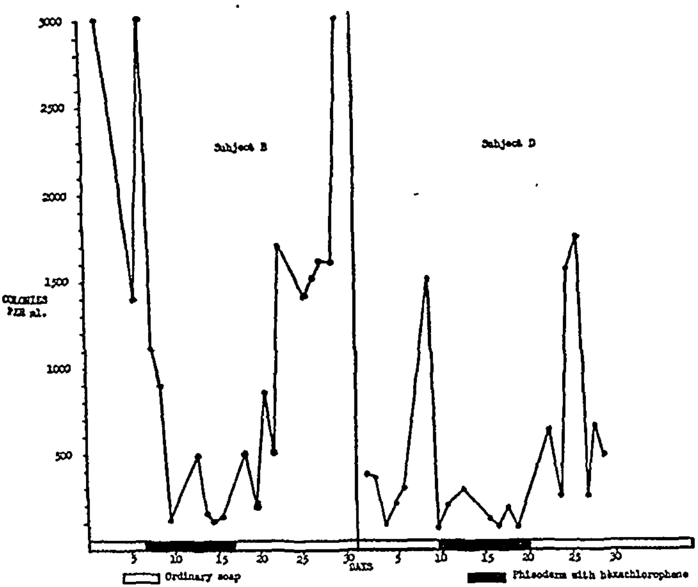
Subject B
Subject D
COLONIES PER ml.
3000
2500
2000
1500
1000
500
5
10
15
20
25
30
DAYS
5
10
15
20
25
30
▭ Ordinary soap
■ Phisoderm with hexachlorophene

FIG. 2

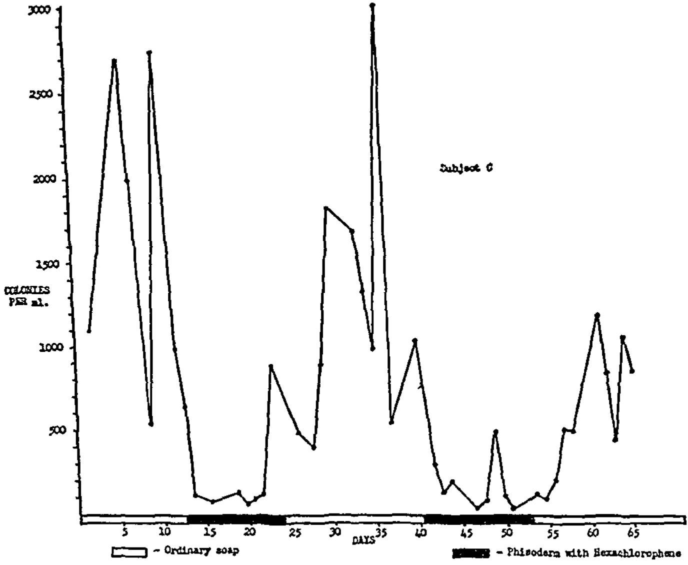
Subject C
COLONIES PER ml.
3000
2500
2000
1500
1000
500
5
10
15
20
25
30
35
40
45
50
55
60
65
DAYS
▭ - Ordinary soap
■ - Phisoderm with Hexachlorophene

FIG. 3

who used one of the methods for the 5 day period. After at least a 10 day interval, the other method of cleansing was then used. The 10 day interval was interposed in order that the skin flora could re-establish itself. In addition, this interval allowed any residual hexachlorophene to be removed from the skin. The results of the study are presented in table 1. This reveals that cleansing with soap containing hexachlorophene for 3 minutes without a brush is superior to the routine 10 minute surgical scrub.

In another aspect of the study, the hands of the subjects were contaminated with a highly virulent culture of hemolytic streptococci. On the day of contamination and on the subsequent 4 days, some of the subjects cleansed with hexachlorophene soap while others used the routine surgical scrub for control observations. Again, after a 10 day interval all subjects used the opposite method for further control observations. The results of this study are summarized in table 2. It should be noted that the hands were contaminated only on the the first day of each week. The persistently high killing effect of the rinsings obtained from subjects using the routine surgical scrub is noteworthy; whereas the mortality rates of mice injected with rinsings from those subjects who had cleansed with hexachlorophene soap rapidly obtained the control level.

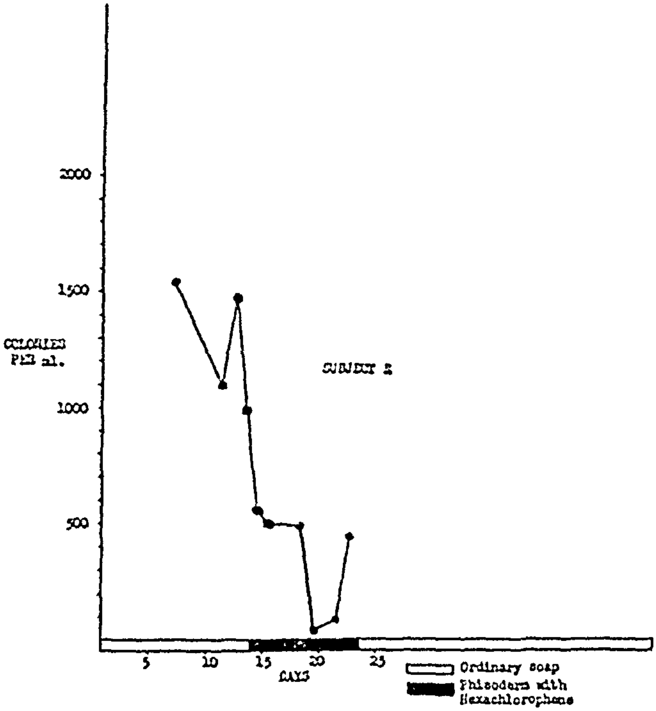

FIG. 4

At present in the operating rooms and surgical clinics at the University Hospital, we are using a 3 minute brushless wash with a detergent, pHisoderm, containing 3 per cent hexachlorophene, G-11. As a supplement to the above experiments we desired to determine the effect of this agent on the skin flora of subjects actively engaged in clinical duties in the urology clinic.

METHOD

Each morning, upon arrival at the clinic, the subjects rinsed their hands for one minute in 1000 ml. of sterile physiological saline. 0.1 ml. of the rinsings were plated and spread on blood agar plates which were incubated for 24 hours. Colony counts were then made. During the work day, for approximately a 2 week period, each subject cleansed exclusively with either ordinary soap or with the pHisoderm-hexachlorophene mixture. The subjects then changed to the alternate agent for a similar period. Such periodic changes in cleansing technique were made throughout the duration of the investigation.

The results are best presented by the charts (figs. 1–4). The shaded areas on the base line indicate the periods during which the detergent-hexachlorophene cleansing agent was used. It should be noted that subject A had used the cleansing agent for several weeks prior to the beginning of the study. Subject B had had no such exposure for at least one month. The others had never used cleansing agents containing hexachlorophene.

Udinsky[5] made frequent colony counts over an 11 month period, during which a soap containing hexachlorophene was used for intervals alternating with those during which ordinary soap was used. Our findings are comparable to his in that a remarkable reduction in skin flora is present when the bactericidal soap is being used. He also made 200 patch tests with hexachlorophene and found no one sensitive. In over a year's use of this agent we have encountered no instances of apparent sensitivity. There has been a striking lack of skin irritation that so often accompanies repeated scrubbing. Clark et al.[3] made interesting studies on the regeneration of skin flora under surgical gloves following the routine surgical scrub and after using a soap containing hexachlorophene. They report a 100 per cent increase in the skin flora during a 45 minute period after the routine scrub whereas after cleansing with a soap containing hexachlorophene, the flora decreased 50 per cent in the 45 minutes during which surgical gloves were worn.

SUMMARY

The evidence presented in these studies demonstrates the superiority of a handwash with an agent containing hexachlorophene over the conventional surgical scrub not only on operating room preparation but also in urological office practice. It is especially significant to the urologist that the antiseptic protection of the hands extends over a period of several days, thus affording both the physician and his patients an insurance against hand borne infection.

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THE SEDIMENTATION RATE IN MUMPS EPIDIDYMO-ORCHITIS

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Candel and his associates in 1944 reported a marked increase in the erythrocytic sedimentation rate with the occurrence of mumps orchitis.[1] He concluded from his series of 37 cases that uncomplicated mumps and mumps encephalitis caused very little change in the sedimentation rate, whereas mumps orchitis caused a marked increase in the rate. This increased sedimentation rate was attributed to either inflammation or degeneration processes occurring within the testes.

There is little information in the literature to indicate supplementary studies which may be used to gauge the severity of the reaction in mumps orchitis. This is probably due to the general concensus that mumps is a childhood disease of little consequence. Diagnosis usually offers little difficulty and when complications do occur the mortality rate is exceedingly low. However, in adult males complicating orchitis occurs in 15 to 25 per cent of the cases, and sterility and impotence, although considered rare, cause the patient much mental anxiety. Some degree of testicular atrophy commonly follows this complication.[2] The authors believe that although the white blood count and temperature may be used quite accurately as an aid in diagnosis, they are not a measure of the severity of the situation. Therefore, the employment of a simple test, the sedimentation rate, may be used as a guide to the severity of the orchitis and may be more closely related to the true significance of the underlying pathological changes.

Uncomplicated mumps is a relatively mild infection generally accepted to be of virus origin. It is characterized by malaise, slight fever, and tenderness at the angles of the jaw. There is subsequently either a unilateral or a bilateral swelling of the salivary glands and consequent trismus. Headache, otalgia, anorexia, nausea and vomiting are not uncommon. The blood picture is in keeping with various other virus diseases, viz., a leukopenia with a relative lymphocytosis, due to the decrease in the polymorphonuclear cells.

Orchitis is a common complication in male patients past puberty. It is usually manifest on the fourth to the eighth day of the disease, accompanied by a recurrence of fever, increased malaise, and swelling of either one or both testicles. The patient appears apprehensive, there is an increase in the pulse rate and there is frequently nausea, vomiting and chills. The patient often complains of pain located in the testicle, the lower abdomen or vaguely in "the groin." Pain may precede the swelling 12 to 36 hours, or it may occur simultaneously with the swelling. In many instances there is no complaint of pain despite considerable swelling. Some patients complain of excruciating pain. The onset of the orchitis is most

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frequently the fourth to the eighth day of mumps, although there is reported in the literature a wide variation from 13 days preceding the parotitis to 44 days after the onset of the parotitis.[3] The fever lasts 3 to 6 days and the swelling of the testicle 5 to 14 days. In a few patients, orchitis with swelling may be the only indication that the patient has mumps.[4, 5]

To date, the laboratory has had little to offer for verification of changes in the body with the onset of orchitis. The leukocyte count ordinarily shows an increase at this time. The serum amylase may be slightly increased, and Applebaum[6] reports an increase in serum amylase in the majority of the cases which he analyzed. The spinal fluid may show a pleocytosis as noted by Candel;[7, 8] but since lumbar punctures are not done routinely, the pleocytosis is not an easily available guide.

TABLE 1. *229 cases of mumps at Southview Hospital 1940 through June 1948*

	CASES	PER CENT
Cases developing orchitis	45	19.8
Total number of males in series	144	62.8
Total number of males in series over 12 years of age	106	46.3
Total number of females in series	85	37.2
Males in series over 12 developing orchitis	45	42.5
Total	229	

TABLE 2. *45 Cases of orchitis*

	CASES	PER CENT
Right side	21	46.7
Left side	10	22.2
Both sides	14	31.1

The erythrocytic sedimentation rate is a relatively simple laboratory procedure and in our experience, has proved a reliable test to verify the occurrence of mumps orchitis. Furthermore, it offers hope of indicating the degree of involvement. To date, no large series of cases has been reported utilizing the test with this thought in mind. One should also remember that the sedimentation rate is of value only if a complete history and physical examination indicate no other disease process existing which could independently increase the sedimentation rate.

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[3] Stengel, A., Jr.: Mumps orchitis. Am. J. M. Sc., 191: 340, 1936.

[4] Dillard, G. J.: Orchitis due to mumps without involvement of the parotid, submaxillary, or sublingual glands. J. M. A. Georgia, 23: 95, 1934.

[5] Zax, E.: Mumps epididymo-orchitis without involvement of the salivary glands, with a case report. Urol. & Cutan. Rev., 41: 624, 1937.

[6] Appelbaum, I. L.: Serum amylase in mumps. Ann. Int. Med., 21: 35, 1944.

[7] Candel, S., Wheelock, M. C. and Grimaldi, G. J.: Mumps orchitis with discussion of plasma prophylaxis. U. S. Nav. M. Bull., 45: 97, 1945.

[8] Candel, S., Wheelock, M. C., Turk, J. P., Jr. and Smoot, J. L.: Mumps meningitis. U. S. Nav. M. Bull., 42: 861, 1944.

TABLE 3

A. The sedimentation rate in 37 cases of mumps

	CASES	AVERAGE SEDIMENTATION RATE	RANGE OF SEDIMENTATION RATE
		mm.	*mm.*
Cases developing orchitis	13	50.6	26–71
Cases without orchitis	24	16.7	4–38

B. 7 cases of mumps in males without complication of orchitis

	CASE	AGE	TEMPERATURE	WBC	SEDIMENTATION RATE
1	J. M.	21	103.6	7,100	22
2	V. J.	15	99.6	5,400	5
3	W. M.	58	99.4	6,650	6
4	D. R.	25	99.8	7,200	4
5	G. K.	9	101.8	6,650	6
6	R. S.	5	?	7,000	20
7	M. F.	30	101.0	7,800	6

TABLE 4. *Thirteen cases of mumps orchitis*

CASE	AGE	TEMPERATURE	WBC	SEDIMENTATION RATE
Right side				
G. M.	26	101.4		53
W. F.	71	99.4	11,450	68
A. K.	49	103.0	7,250	48
N. K.	33	102.8	8,000	54
H. S.	40	99.8	14,200	35
Left side				
S. S.	25	100.6	11,100	26
E. P.	35	102.0	7,450	22
G. H.	21	102.8	6,650	57
Bilateral involvement				
C. B.	28	99.6	11,550	71
E. S.	39	103.4	12,500	69
F. S.	30	105.0	12,000	60
D. O.	18	105.0	12,500	39
S. B.	20	103.0	5,050	47

For the present study, 229 cases of mumps admitted to Southview Hospital from 1940 through June 1948 have been reviewed (table 1). In this series there were 45 cases of epididymo-orchitis as a complication of mumps (table 2). In 1947 and the first 6 months of 1948 there were 37 cases of mumps with laboratory data including a sedimentation rate determination (table 3, *A*). Of these, there were 13 cases of epididymo-orchitis and 24 with no complicating orchitis; thus affording some opportunity for a comparison (tables 4 and 5; fig. 1).

As a matter of interest, in the total cases there were 85 (37.2 per cent) female patients, 3 of whom showed definite signs and symptoms of oophoritis. Two others were pregnant, and 1 required extensive treatment to maintain the pregnancy (table 1).

TABLE 5. *Twenty-four cases of mumps without complicating orchitis*

Eighteen cases of uncomplicated mumps

	CASE	SEX	AGE	TEMPERATURE	WBC	SEDIMENTATION RATE
1	G. H.	F	26	100.0	8,200	38
2	H. T.	F	20	99.6	8,950	29
3	I. E.	F	19	99.8	8,500	5
4	M. S.	F	19	100.2		20
5	J. M.	M	21	103.6	7,100	22
6	M. H.	F	6	100.0	5,600	24
7	J. Z.	F	4	100.0	8,200	15
8	D. T.	F	13	101.2	4,350	23
9	V. J.	M	15	99.6	5,400	5
10	W. M.	M	58	99.4	6,650	6
11	R. D.	F	7	102.4	6,250	19
12	D. R.	M	25	99.8	7,200	4
13	A. T.	F	19	101.2	6,850	9
14	G. K.	M	9	101.8	6,650	6
15	D. F.	F	35	103.4	6,200	25
16	P. S.	F	10 mos.	102.6	8,100	25
17	R. S.	M	5		7,000	20
18	M. F.	M	30	101.0	7,800	6

Six cases of mumps with complications causing increased sedimentation rate

	CASE	SEX	AGE	TEMPERATURE	WBC	SEDIMENTATION RATE	COMPLICATION
1	A. B.	F	20	98.6	14,100	57	Immediate postoperative period
2	D. M.	M	60	101.8	16,600	67	Active arthritis
3	A. C.	F	16	100.2	?	61	Six months pregnant
4	C. B.	M	60	99.6	?	140	Cirrhosis, cardiac
5	L. D.	F	26	99.4	4,500	53	Four to five months pregnant
6	A. T.	F	4	102.8	9,850	65	Concurrent scarlet fever

There were also 10 cases of mumps meningo-encephalitis, only 1 of which had an accompanying orchitis. Six patients showed evidence of pancreatitis; and 1, mastitis.

One hundred and forty-four (62.8 per cent) patients were males of whom 106 (46.3 per cent) were either 12 years of age or older. In other words, there were 106 patients in the age group "eligible" to have mumps epididymo-orchitis.

Orchitis occurring before puberty is considered exceedingly uncommon. Of these 106 patients there were 45 cases (42.5 per cent) as evidenced by 1) elevated temperature above that expected in simple cases of mumps, 2) swelling of either one or both testicles, and 3) pain which varied tremendously in intensity and location. A number of cases showed considerable swelling without subjective pain. Although only 20 per cent of all of these cases showed orchitis, 42.4 per cent of the male patients over 12 developed mumps orchitis (table 1).

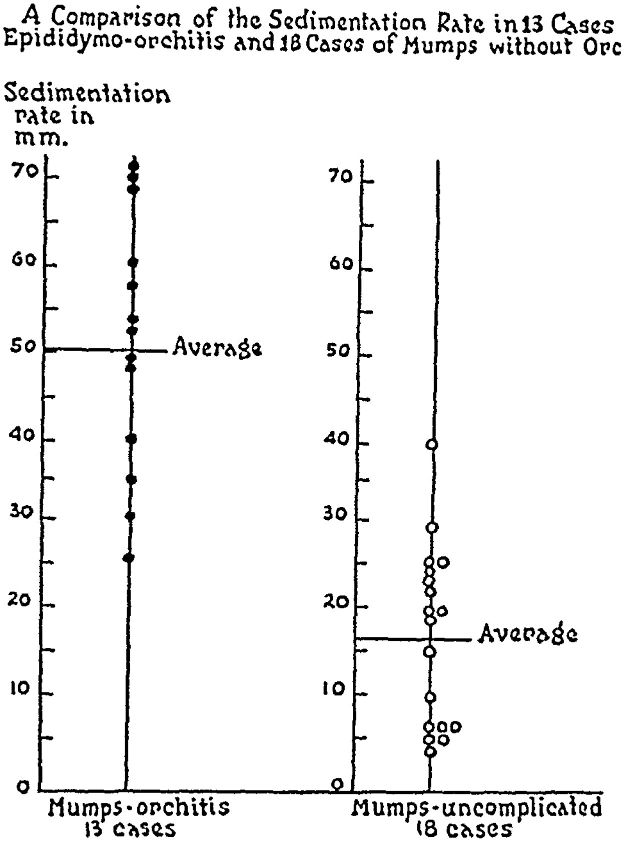

FIG. 1

Approximately 70 per cent of the cases of orchitis were unilateral and the right side was involved twice as frequently as the left. The figures are as follows (45 cases from entire series):

	cases	*per cent*
Involvement of right side only	21	46.7
Involvement of left side only	10	22.2
Involvement of both sides	14	31.1

The youngest patient in the series who contracted mumps epididymo-orchitis was 15 years of age and the oldest was 71 years; the average age being 28.8 years. The total leukocyte count varied from 2,800 to 14,200 cells. The temperature on admission ranged from 99.4 to 106.2 F. The amount of temperature and the leukocyte count showed no relation to the amount of swelling, intensity of pain, or to the length of time required for recovery. In a majority of the cases, however, there occurred a noticeable elevation of the temperature of 1 to 3 degrees preceding actual swelling of the testicles. Generally there was noted a mild increase in the total leukocyte count either at this time or immediately following the onset. These changes were noted most frequently between the third and the eighth day of mumps.

The Westergren method was utilized in the determination of the sedimentation rate. A rate of 4 to 16 mm./hr. was considered normal, 16 to 24 mm./hr. was considered a mild abnormality and anything above 24 mm./hr. was considered definitely abnormal.

The average sedimentation rate for 13 cases of orchitis at Southview Hospital during the past year was 50.6 mm./hr. The average for 18 uncomplicated cases of mumps observed over the same period of time was 16.7 mm./hr. Due to the small number of cases which had sedimentation rates performed as a part of their case study, the following patients were included in the 18 cases: 1) 7 males with no complications, with average sedimentation rate of 9.9 mm./hr. (table 3, *B*); 2) 11 females with no apparent complications, and average sedimentation rate of 21.5 mm./hr. Six cases were eliminated from the series because of accompanying medical conditions which could increase the sedimentation rate (tables 4 and 5). The average sedimentation rate for right testicular involvement was 51.2 mm./hr.; with left sided involvement, the average was 38.0 mm./hr. Bilateral involvement resulted in an average of 56.5 mm./hr. It may be assumed from this that the sedimentation rate tends to show the total amount of involvement. This premise is further substantiated in the case of several patients who had appreciable pain either in the groin or testicles, without swelling. In these cases, the sedimentation rate was noted to be within normal limits, and it is assumed that the orchitis was aborted in some manner, since they failed to exhibit any testicular swelling and the pain disappeared within a matter of hours. The total leukocyte count and the degree of the temperature varied tremendously with the patient and could not be taken as a consistent indication of either the intensity of pain or the degree of involvement. There was no relationship of either white blood count or temperature to the sedimentation rate.

It has not been possible to follow any of our patients sufficiently long to determine the time required for the sedimentation rate to return to normal, but a definite decrease in the rate was noted by the time the patient was ready for release from the hospital. This coincided with a reduction in testicular swelling. No relapses in this group have been reported.

Treatment has been purely symptomatic. For pain, such conservative measures as salicylates and/or codeine, and support of the testicles by a tape bridge with local application of cold packs have given gratifying results. No cases were encountered with pain severe enough to require incision of the scrotum and tunica albuginea, as advocated by Wesselhoeft.[2, 9] The patients were allowed bathroom privileges unless their temperature showed either an upward trend or was maintained above 103 F, or if such activity caused them too much discomfort. When the testes were normal in size, the patients were allowed to return to normal activity over a period of several days. Mumps convalescent serum was used only

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[9] Wesselhoeft, C.: Mumps. New Eng. J. Med., 226: 530, 1942.

on those patients who had marked febrile reactions and who showed symptoms resembling an approaching encephalitis.

According to available pathological reports of specimens seen at surgery and in those cases in which biopsy has been possible, either the testicles or the epididymis or both are involved.[2, 3, 4] They may be involved either simultaneously or separately. In the more severe cases hydrocele is common and there is edema of the scrotum, tunica albuginea, intertubular connective tissue, and some groups of seminiferous tubules. Destruction of the seminiferous tubules only occurs in the involved areas. There may be small areas of hemorrhage and/or fibrin formation. Many polymorphonuclear leukocytes and endothelial leukocytes infiltrate between the tubules. In many places it appears as if the process was extending from the peritubular connective tissue of the circumference of the tubule by involving only a small portion of the circumference. In addition to the edema of the tunica albuginea, there are small hemorrhages and zones of cellular exudate about many blood vessels. It is the resistance of the tunica albuginea that appears to be responsible for the pain, and often the pressure necrosis that subsequently leads to testicular atrophy. Liquefaction necrosis is not present in any of the structures. This apparently leads to a slight shift from a comparative lymphocytosis to a mild polymorphonuclear leukocytosis which is comparatively rare in any other of the complications of mumps. The spermatic cord is often tender and diffusely swollen up to the external inguinal ring, and pressure over the adjacent abdominal wall elicits pain.

Whereas in mumps involvement of the parotid gland the inflammatory reaction is evident, involvement of other salivary glands, the pancreas, ovaries, or even the onset of an encephalitis, a silent inflammatory reaction may not be recognized. However, this appears to be the true pathological picture in mumps orchitis. It is thought that with the involvement of the male gonads an intracellular change occurs following the edema which disturbs the albumin-globulin fraction in the tissue fluid, probably by increasing the globulin and reducing the albumin in the plasma. The process is thought to occur in the plasma rather than the red blood cells and causes the red cells to show a marked increase in rouleaux formation with a resulting increase in the sedimentation rate.

SUMMARY AND CONCLUSIONS

Two hundred and twenty-nine cases of mumps have been reviewed, 45 of which were complicated by epididymo-orchitis.

The clinical and pathological picture of this complication has been briefly discussed.

In a study and analysis of 37 cases, the sedimentation rate was found to be markedly increased when epididymo-orchitis was present.

The sedimentation rate affords a better insight as to the true pathological picture than temperature elevation and leukocyte count. Sedimentation rate may be of value in showing the relative amount of testicular involvement.

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CLINICAL APPLICATION IN UROLOGICAL SURGERY OF A NEW CONCEPT OF THE PHYSICO-CHEMISTRY OF PATHOLOGICAL LESIONS[1]

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The urological surgeon encounters a variety of problems, some of which are more or less peculiar to the field, while others are encountered in all types of surgery. As in all surgical procedures, there is always the problem of pain produced by the trauma of the surgical attack upon the pathological process. Pain after routine cystoscopy is a common problem and postoperative pain is encountered in all types of kidney and ureteral operations. In prostatic surgery, the control of postoperative pain is complicated by the advanced age of the patients.

Without a better understanding of the processes of wound healing, little can be done to facilitate the reparative process and to relieve symptoms except in a supportive fashion. The research and concepts of Revici concerning the physicochemical alterations within abnormal tissues suggest certain methods of approach to these common postsurgical problems.[2]

In order to understand the considerations that have led to the present clinical study, a brief description of Revici's theory of the pathogenesis of abnormal foci is necessary.

Revici and others have studied pain in various pathological conditions. They have found that variations in pain intensity are correlated with alterations in acid-base balance of the body, as reflected by the urinary *p*H.[3, 4, 5] By correlating the *p*H values of hourly urine specimens with hourly evaluations of pain intensity made by the patient, two distinct pain patterns have been demonstrated. In one type, pain and urinary pH are found to vary in a parallel fashion, pain becoming more intense as the urine becomes more alkaline, and less severe as the urine becomes more acid. This type is called "alkaline pain." Figure 1, *A* is a typical curve of a case with "alkaline pain."

In "acid pain," an inverse relation is present. The pain is most intense when the urine is most acid and less so when the urine is more alkaline (fig. 1, *B*). These findings suggest that spontaneous pain is the result of local acid or alkaline changes which are augmented or neutralized by the general acid-base balance. Other authors have emphasized the importance of local chemical or physicochemical changes in the production of pain. The pain of intermittent claudication and local tissue trauma have been attributed to local physicochemical changes.[6]

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[1] Research supported in part by the Cancer Research and Hospital Foundation.

[2] Revici, E.: The oxybiotic dysequilibriums in biology: Role of lipids. Monaco-Mediterranee Med., 8th year, extra supplement: 1, 1941.

[3] Revici, E.: The pathogenesis of the painful focus. Pasteur, 15: 33, 1942.

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[5] Revici, E., Huesca, C. and Ravich, R. A.: Correlations between pain and acid-base balance of the body. To be published.

[6] Lewis, T.: Pain. New York; MacMillan, 1942.

The chemical and physicochemical changes giving rise to pain in ischemic limbs have been studied.[7, 8]

Revici has shown that strong acidifying agents intensify "acid pains" but relieve "alkaline pain." On the other hand, alkalinizing substances decrease acid pain and aggravate alkaline pain.[3] Others have administered alkalinizing agents systemically to reduce the pain of angina pectoris and intermittent claudication[9] and locally to control pain in painful abscesses.[10]

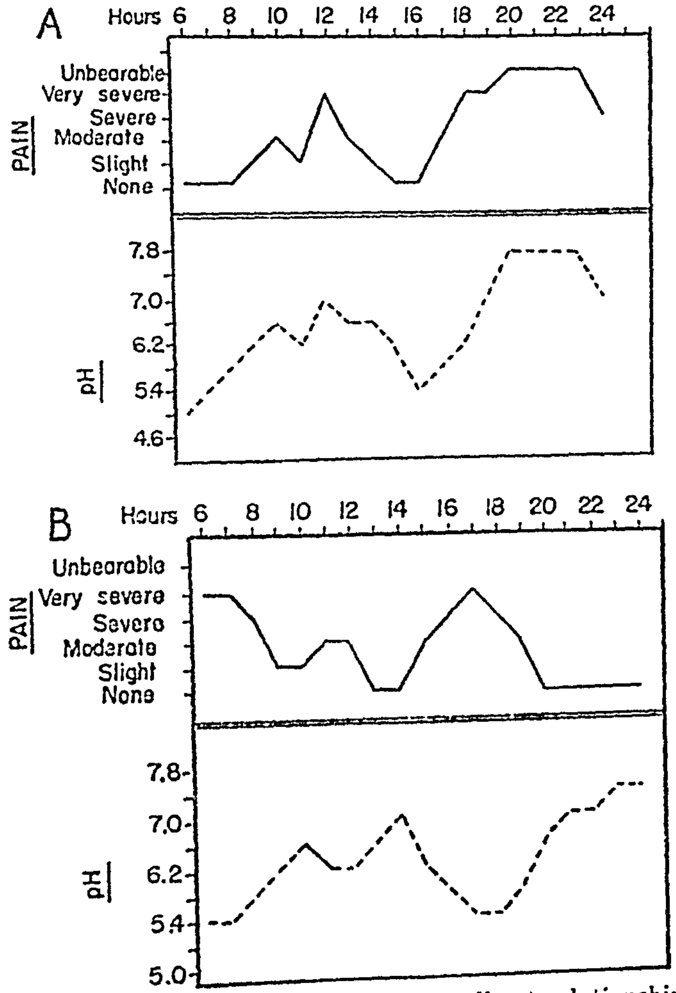

FIG. 1. *A*, typical "alkaline pain" curve, showing direct relationship between hourly variations in intensity of pain and urine pH. *B*, typical "acid pain" curve, showing inverse relationship between hourly variations in intensity of pain and urine pH.

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[7] Maison, G. L. and Forster, A. C.: pH changes in ischemic muscle after voluntary contraction. Am. J. Physiol., 125: 735, 1939.

[8] Harpuder, K. and Stein, I. D.: Studies on the nature of pain arising from an ischemic limb. I. Clinico-experimental observations. II. Biochemical studies. Am. Heart J., 85: 429, 1943.

[9] Katz, L. N., Lindner, E. and Lanet, H.: On the nature of the substance(s) producing pain in contracting skeletal muscle: Its bearing on the problems of angina pectoris and intermittent claudication. J. Clin. Invest., 14: 807, 1935.

[10] v.Gaza, W. and Brandi, B.: Relation between hydrogen-ion concentration and pain; interpretation of ischemic and inflammatory pain. Klin. Wchnschr., 5: 1123, 1926.

Further studies have been carried out upon accessible painful malignant growths,[3] and have indicated that the pain is associated with local disturbances in tissue *p*H. Thus painful tumors that produce "acid pain" are found to have a local *p*H below that of surrounding normal tissues, while in tumors that produce "alkaline pain," the local *p*H is higher than that of the surrounding areas. Pain is more severe when these deviations from the norm are spontaneously or artificially increased.

As a result of these observations, spontaneous variations in pain intensity are attributed to the interaction of two factors: a) the local production of substances causing local *p*H changes and b) the ability of the general body reaction to neutralize these deviations.

Acid pain was found to occur as a result of the local accumulation of lactic acid in abnormal amounts, thereby altering the *p*H of the pathological focus. Alkaline pain was found to be associated with lesions in which the *p*H was increased by accumulation of alkaline sodium compounds.[3]

Revici places considerable emphasis upon the rôle of lipids in the production of these physicochemical changes. He states that there is an apparent increase in the cholesterol and unsaponifiable lipid fraction and a concomitant decrease in the fatty acids in lesions producing acid pain, whereas the opposite conditions exist in lesions with alkaline pain.[2] He has classified lipids according to their alkaline or acid radicals as lipobases or lipoacids and offers evidence that these two classes of lipids are mutually antagonistic both in vitro and in vivo. Lipobases and lipoacids are antagonistic in their effects upon painful focal lesions. Lipobases decrease the pain of lesions producing alkaline pain, but increase an acid pain. On the other hand, lipoacids are found to aggravate alkaline pain and to diminish acid pain.

TABLE 1

1) Lipobase predominant → acid substances (lactic acid) → lower tissue *p*H → acid pain. ℞—alkalinizing agents or lipoacids.

2) Lipoacid predominant → alkaline substances (alkaline sodium salts) → higher tissue *p*H → alkaline pain. ℞—acidifying agents or lipobases.

Table 1 summarizes Revici's concept of the physio-pathology of abnormal foci.

Revici defines a lipid as a substance composed of apolar and polar groups in which the chemical and physical characteristics of the substance are determined primarily by a predominance of the apolar group. Thus he includes substances such as the higher alcohols, the higher amines, mercaptans and sulfonates under the general heading of lipids and utilizes them as lipobases or lipoacids depending upon the nature of the polar group.

While in many pathological conditions, careful analysis is required to determine the physico-chemical characteristics of the lesion, in their initial stages, traumatic wounds are apparently invariably of the type in which lipoacids are predominant. According to his theoretical concept therefore, administration of lipobases may produce beneficial results if it is assumed that the maintenance of a lipobase-lipoacid equilibrium is desirable (table 1).[2]

CLINICAL EVALUATION

Since the possible implications of this concept of the local pathological focus are extremely broad, a program has been undertaken to determine the clinical value of such a concept. One part of this program has been directed towards an evaluation of the concept in relation to the trauma of surgical intervention and its sequelae. The study of its application in urology will be discussed here.

As indicated above, the inflammatory response to trauma is considered to involve a disturbance in cellular lipids in which the lipoacids are increased in relation to the lipobases. This leads to a local increased alkalinity due to accumulation of alkaline sodium salts. These chemical and physicochemical changes in turn produce stimulation of nerve endings that lead to what has been described as alkaline pain.

Since the disturbance in the lipid balance within the pathological areas is felt to be the basic factor, correction of the disturbance by administration of lipobase has been the aim in these studies. n-Butanol has been employed as the lipobase in all the cases discussed.

Choice of lipobase. n-Butanol is the lowest member among the monohydric alcohols that is a lipobase according to Revici's classification. Its formula is: $CH_3(CH_2)_3OH$. This chemical was chosen by him as a representative lipobase because of its ease of administration by all routes, its very low toxicity and the absence of undesirable side effects.[11, 12, 13]

Administration of n-butanol. The method of administration of n-butanol will be discussed only briefly here because interest has been directed primarily towards determining whether in actual clinical experience, this substance as a representative lipobase is of value. It may be that other lipobases will prove more active than n-butanol. Furthermore, no effort has been made to determine the most effective dose schedules, the aim being merely to administer sufficient amounts to observe clinical effects, if any.

An 8 per cent solution of n-butanol in saline was used in 5–10 cc doses given intramuscularly. This dose was given 10 minutes before cystoscopy. In the major surgical procedures, n-butanol was administered the night preceding and 1 hour before operation. During the first few postoperative days, it was also given every 1 to 4 hours as indicated by the degree of pain or bleeding. The frequency of administration was decreased gradually and eliminated entirely by about the tenth day. In all the major operative procedures, 60 cc of the stock 8 per cent solution were also administered intravenously in 2000 cc 5 per cent glucose in physiological saline given routinely to all cases immediately after operation. No ill effects were observed in any of the cases that received n-butanol.

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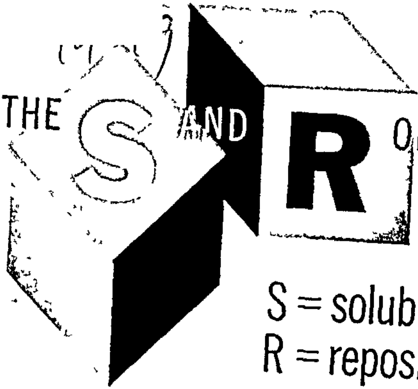
[11] v. Oettingen, W. F.: The aliphatic alcohols: their toxicity and potential dangers in relation to their chemical constitution and their fate in metabolism. U. S. Public Health Bull. No. 281: 122, 1943.

[12] Ravich, R. A. and Revici, E.: Toxicity of n-butanol. To be published.

[13] Revici, E. and Ravich, R. A.: Unpublished data.



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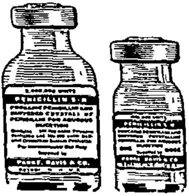

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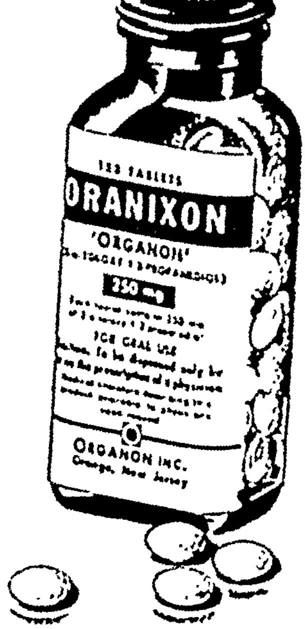

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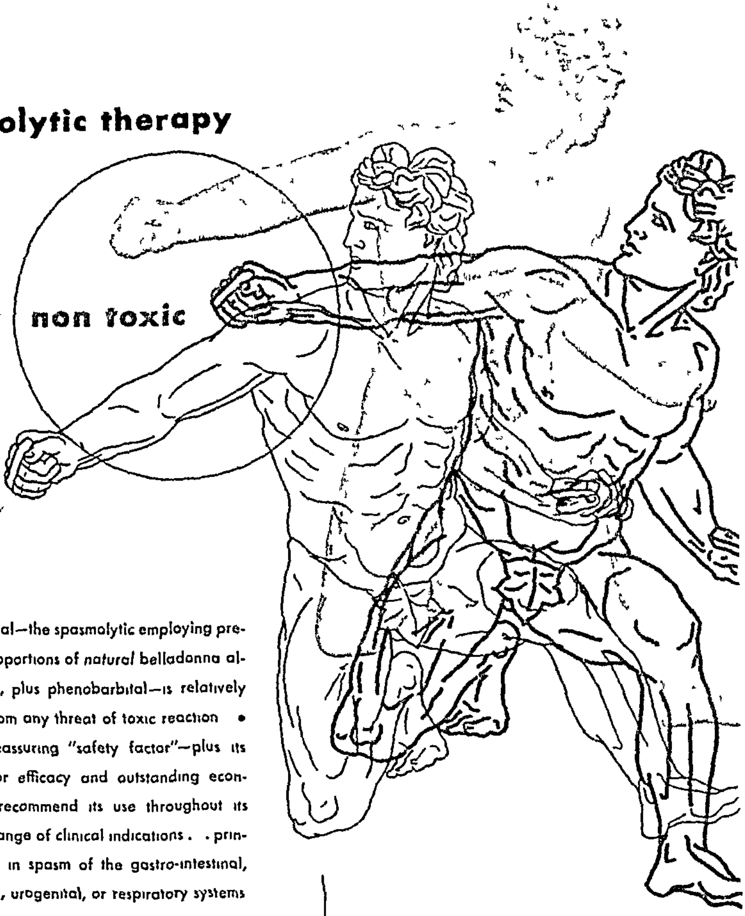

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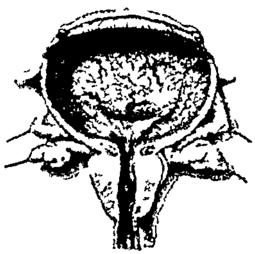

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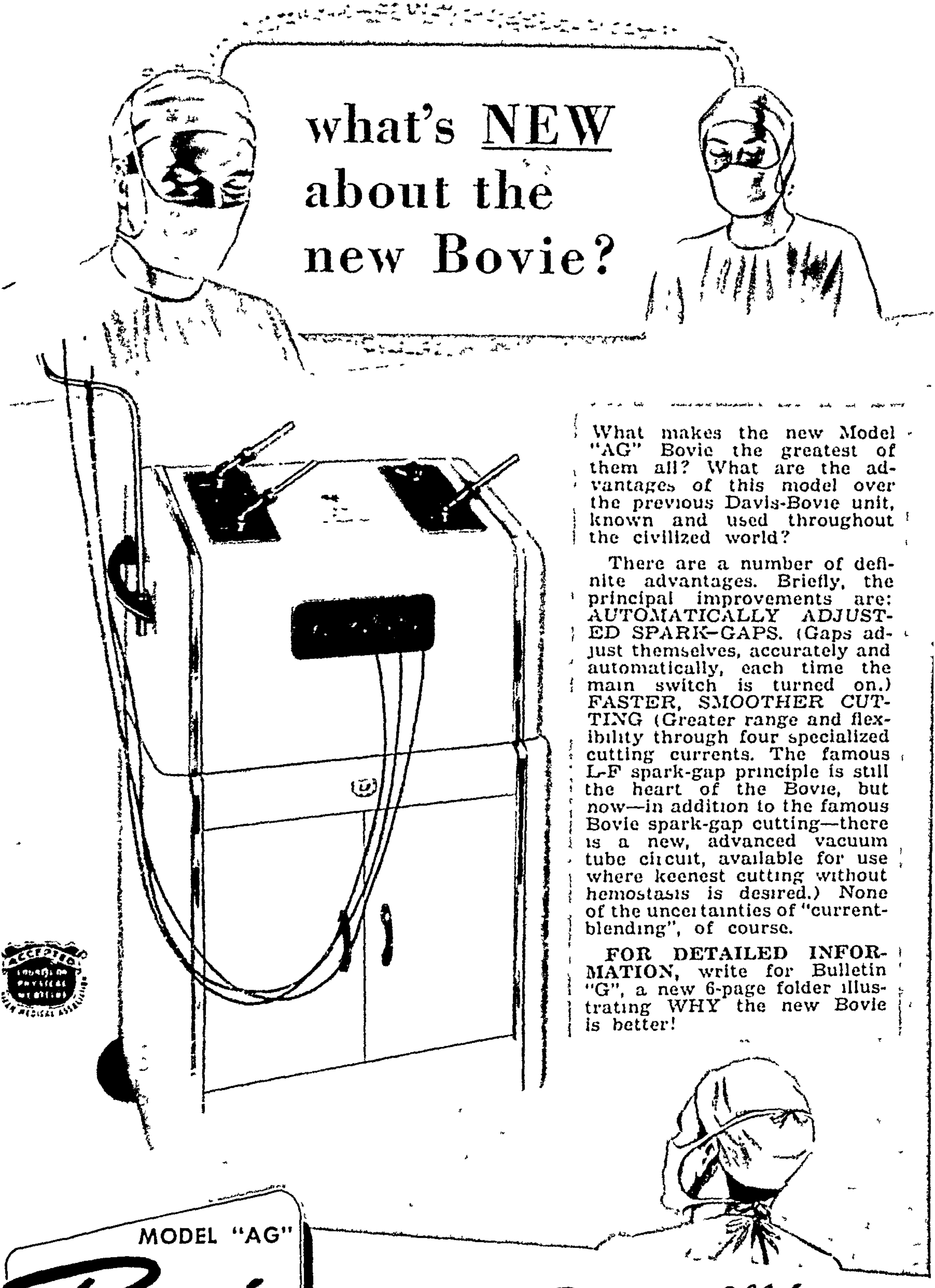

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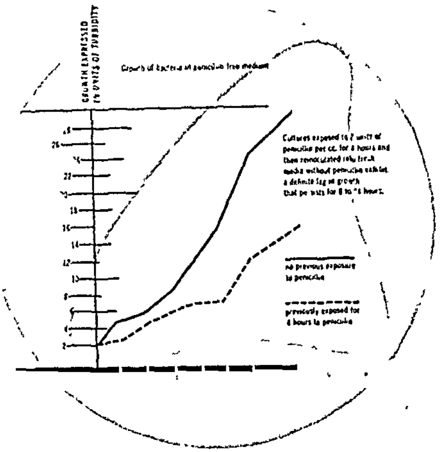

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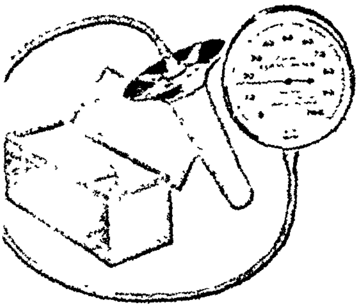

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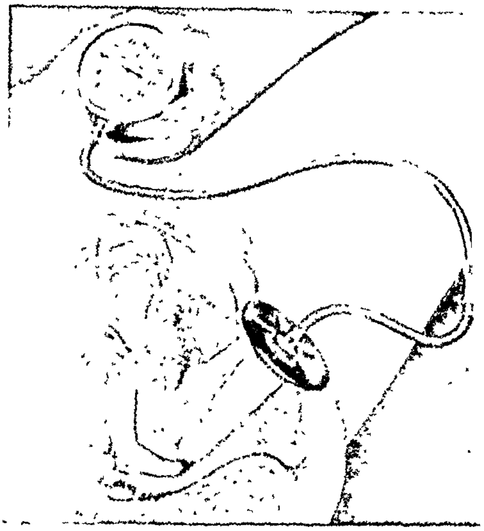

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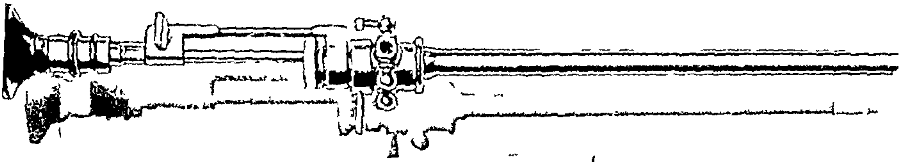

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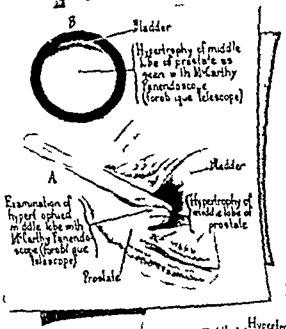
B
Bladder
Hypertrophy of middle lobe of prostate as seen with McCarthy Panendoscope (foroblique telescope)
Bladder
A
Examination of hypertrophied middle lobe with McCarthy Panendoscope (foroblique telescope)
Hypertrophy of middle lobe of prostate
Prostate

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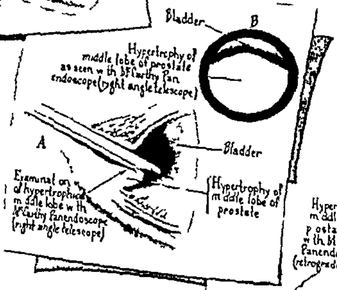
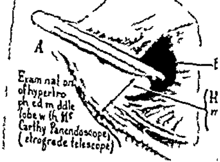

Bladder
B
Hypertrophy of middle lobe of prostate as seen with McCarthy Panendoscope (right angle telescope)
A
Bladder
Examination of hypertrophied middle lobe with McCarthy Panendoscope (right angle telescope)
Hypertrophy of middle lobe of prostate


Hypertrophy of middle lobe of prostate as seen with McCarthy Panendoscope (retrograde telescope)
A
Examination of hypertrophied middle lobe with McCarthy Panendoscope (retrograde telescope)

The sectional views above and at right show clearly the possibilities of accurately interpreting the extent of prostatic hypertrophy and its relation to the vesical orifice.

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ADRENAL CORTICAL TUMOR: CASE REPORTS[1]

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We wish to present case histories of 2 patients with adenoma of the adrenal cortex We think they will be of interest because each patient is representative of a different clinical group One patient had symptoms characteristic of that group in which the metabolic functions of the adrenal cortex are disturbed, the second patient is illustrative of the group in which the genital symptoms are most altered

The adrenal cortex has many functions which are carried out through elaboration of endocrine products, of which more than twenty compounds have thus far been isolated and chemically identified These functions of the adrenal cortex fall into two main groups The first is the metabolic, through which salt concentration, fat and carbohydrate metabolism and water balance are controlled The second group includes hormone effects on the entire endocrine system and on the genital system in particular, so much so that the adrenal cortex has been called a genital gland There are also effects on blood pressure, kidney function and general bodily vigor which are not as yet accurately evaluated While the effects on the genital system are the most striking, it is the effects on the metabolic processes which are essential to life, and it is, as we shall see, the disturbance of these metabolic functions which is most dangerous to the patient

Adrenal cortical tumors can affect the patient's well being in two ways: as tumors, per se, inasmuch as they can be or become malignant and invade other organs and metastasize In the second way they affect the patient through the hormones which the tumor cells elaborate Adrenal cortical tumors show many varieties of clinical syndromes, depending upon which of the many functions are altered We will discuss these later

CASE REPORTS

Case 1 J D , R&E No 338 975, was a white female infant 9 months of age Birth had been at full term, with normal uncomplicated delivery, birth weight was 8 pounds 5 ounces There was no history of endocrine disturbance in the parents or two siblings At the age of 2 months it was noticed that the child had a bloated appearance and had begun to gain weight excessively At about the same time a few hairs were noted in the genital region The family physician recommended endocrine study, but because the child was "good natured" and did not seem uncomfortable, the parents had delayed further examination At the time of admission the child weighed 27 pounds and had a temperature of 103 F, the blood pressure was 140/90 The child appeared extremely obese and there was an acne like rash on the forehead and cheeks (fig 1) There was some fine and coarse hair in the interscapular region of the back and also over the genitalia. There was some pharyngeal infection and signs of a diffuse pneumonic process in the lungs. No abdominal masses were felt. The clitoris did not seem to be enlarged.

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[1] Read at annual meeting, North Central Section, American Urological Association, Des Moines, Iowa, October 30, 1948

The blood count showed red blood cells 5.3 million, hemoglobin 13 gm., hematocrit 45, white blood cells 18,000.

The nonprotein nitrogen was 36 mg. per cent; serum calcium 11.3 gm.; phosphorus 5.5 mg. Alkaline phosphatase 5.3 Bodansky units. Serum chloride 628 mg. Serum sodium 136 milliequivalents.

Roentgenograms of the skull showed a normal sella turcica. Roentgenograms of the chest were normal. Roentgenograms of the bones showed normal findings. An intravenous urogram was unsatisfactory and because of the child's illness, no opportunity was afforded to repeat this roentgenogram or to do a perirenal air injection. The routine urine findings were negative. Two determinations of 24 hour 17-ketosteroid level showed 2.7 mg. on one determination and 1.9 mg. on another.

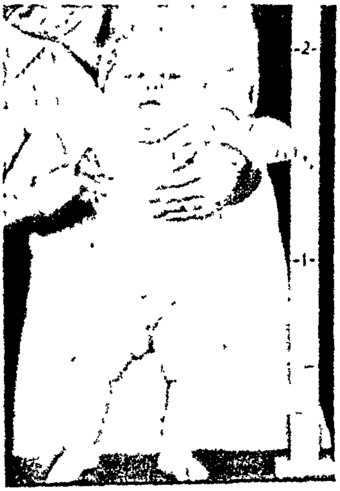

FIG. 1. Case 1. Patient at time of admission

Diagnosis of endocrine disturbance with possible adrenal cortical tumor and acute upper respiratory infection was made.

Penicillin was given and the temperature finally returned to normal 6 days after admission and remained normal for about a week, during which time the endocrine study was begun. This could not be completed, however, as on the thirteenth day after admission the patient began to have fever and diarrhea. The fever fluctuated, and sulfonamides as well as other antibiotics were given, but the diarrhea persisted in spite of all therapy. The clinical course was downhill and the patient expired 5 weeks after admission to the hospital.

At autopsy the lower lobes of both lungs showed considerable congestion. The kidneys were normal. The uterus was infantile and showed an immature endometrium. The ovaries were normal in size but there was some degree of maturity of follicles. The thyroid was apparently normal. Examination of the head was not permitted. The right adrenal was grossly normal, weighed 4½ gm., and showed a normal histologic picture. The left adrenal weighed 17 gm. and was almost completely replaced by a well encapsulated, mottled brownish yellow mass, moderately firm in consistency. This on section showed small, well demarcated yellow areas; around the periphery of the tumor compressed normal adrenal tissue could be made out. Histologic section of this tumor showed many large areas of necrosis and some areas of fibrosis and hemorrhage. Intact portions of the tumor showed extremely pleomorphic cells, many very large and bizarre in character. The eosinophilic cytoplasm was homogeneous and quite clear. Nuclei of the cells were often very hyperchromic and variable in size and shape. There were some multinucleated giant cells. After careful and prolonged search, however, no mitotic figures could be found. The tumor was apparently separated from the normal gland by a thick fibrous capsule. No special stains were made.

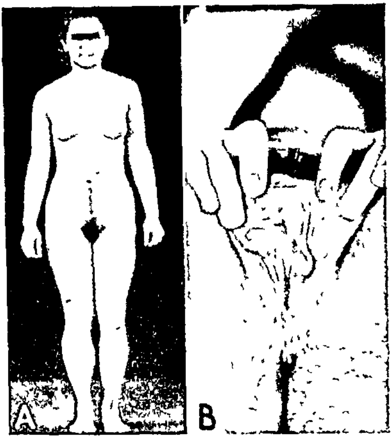

FIG. 2. Case 2 *A*, patient at time of admission, *B*, close-up of genitalia.

Case 2. A. B., R&E No. 342–357, a 17 year old white girl, gave a history of amenorrhea of 2 years' duration. The menarch had occurred at the age of 13 and the periods had been irregular for 2 years, after which time, at the age of 15, they had stopped altogether. At about the same time the patient began to note the growth of dark facial fair. This became progressively thicker and at the time of admission was quite heavy. Several months prior to admission another surgeon had done an exploratory abdominal operation and an appendectomy, with the thought that the patient might have an arrhenoblastoma. The ovaries were examined and sections taken, but were reported as simple cysts. At the time of this operation it was said that an attempt had been made to palpate the adrenal glands but that no tumor had been found.

On admission the patient appeared alert, intelligent, weighed 148 pounds and was 5 feet, 5 inches tall. The blood pressure was 90/70. The face showed a heavy growth of coarse black hair, as did also the lower arms, buttocks and particularly the genital area (fig. 2). She had shaved her legs but not her face. Her voice was low in register although the larynx was not visibly prominent. The thyroid was not palpably enlarged. The skin showed no striae and no cyanosis or edema. The breasts were moderately well developed and showed some periareolar hair. She said they had not changed in size during the previous 2 years. Pelvic examination showed the clitoris to be moderately enlarged. There was some vaginal discharge present. Pelvic examination showed no abnormal findings. Vaginal and cervical smears were taken. The vaginal cells were reported as showing poor estrogenic level with numerous small cells resembling atrophic and androgenic types; endometrial cells were not remarkable. No masses could be felt on abdominal examination and no tenderness was elicited.

Laboratory examination showed red blood cells 4.3; hemoglobin 16 gm., hematocrit 44, white blood cells 7,100, Kahn and Wassermann negative. The nonprotein nitrogen was 30 mg., CO_2 combining power 52. On the Exton-Rose tolerance test the fasting glucose was 71 mg.; ½ hour, 143 mg.; 1 hour, 157 mg. Cholesterol 199 mg. Sodium chloride, 4 determinations, all between 480 and 500 mg. Serum sodium 324 milliequivalents. Serum potassium 19.7 milliequivalents. Albumin 5.0 gm. Globulin 2.5 gm.

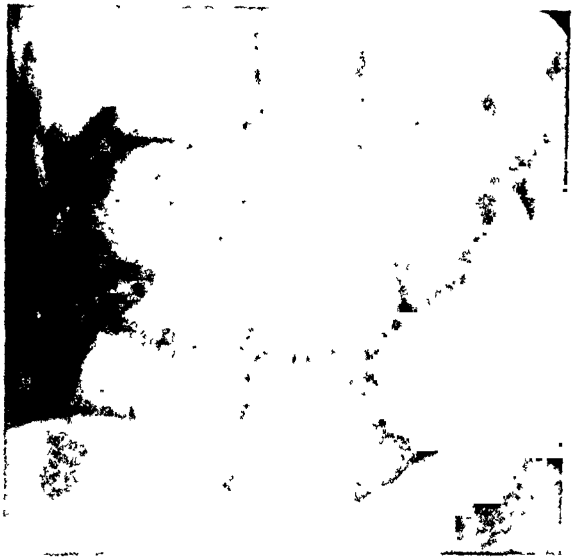

FIG. 3. Case 2. X-ray taken after perirenal air insufflation, showing tumor above right kidney.

Roentgenograms of the chest were normal. Roentgenograms of the skull and of the long bones were normal. Visual fields were examined and were normal. An intravenous urogram showed prompt dye output on both sides. Outlines of the kidney pelves were normal; however the right was evidently depressed from its normal position. Perirenal air insufflation confirmed the presence of a tumor and showed a well outlined mass in the region of the right renal gland (fig. 3). Seventeen-ketosteroid determinations on two occasions showed 88 mg. and 90 mg. output in 24 hours.[2] The determination of the 11-oxy or corticoid group showed 5.8 mg. in 24 hours.

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[2] Determination of 17-ketosteroids were made by Dr. K. S. Appa, of the Department of Medicine.

At operation the tumor was approached by a lumbar incision through the bed of the twelfth rib, which was resected. The tumor was easily identified and seemed to be apparently well encapsulated. Traction downward on the kidney aided in the exposure and freeing of the tumor mass The vessels at the lower end were easily isolated, clamped and cut. However, there were some vessels at the upper pole near the diaphragm which could not be easily reached and in attempting to put a clamp blindly on these vessels, the tumor was squeezed and the capsule ruptured with loss of some of the tumor contents. Even despite this, there was some troublesome bleeding from vessels emerging immediately under the diaphragm and which could only be caught after the tumor was removed. The wound was very thoroughly lavaged with saline solution to remove any loose cellular material. Two doses of 2 cc each of cortical extract were given just before surgery, 1 cc were given during the operation and 2 cc later the same day. There was no postoperative reaction of note and the entire post-surgical course was uneventful

DISCUSSION

Case 1, that of the infant, illustrates the type of hyperactivity of the adrenal cortex affecting the metabolic functions, especially those of fat, sugar and water metabolism The child was remarkably obese and, as mentioned, even the parents noticed what they described as a "water-logged" appearance. Genital changes, although present, were not prominent. There was almost no resemblance to the picture of precocious virilism as seen in the more common bilateral hyperplasia.

Associated with these metabolic changes is a lack of resistance to various types of stress, including infectious disease It was this lack of resistance which indirectly led to the child's death Two intercurrent infections, first an upper respiratory infection and then an intestinal one were the proximate causes. In a normal child such common conditions are controlled without difficulty

If a tumor caused a mere increased secretion of the normal hormones, one would expect the child to be more resistant to stress than normal. Obviously such is not the case and the changes are not that simple There is increased output of some hormone products at the expense of others so that, although the total amount of secreting tissue is increased by the tumor, there may be a deficiency of essential fractions and consequent deficiency symptoms The clinical pictures produced vary considerably depending on which functions are accentuated and which are diminished

Case 2, the teen-age girl, presented severe genital disturbance, tending towards masculinization. However the virilizing changes were not so severe as those seen in congenital bilateral hyperplasia. The breast contours were not lost, neither were the general female body contours or the genitalia essentially altered. This is readily explained when we consider that the endocrine alterations were of only 2 years' duration, and that childhood and pubertal development was presumably under normal influences On the other hand, in bilateral hyperplasia the abnormal influences are active during the entire pre- and postnatal periods when sensitivity to such influences is greatest

In case 2 there was no evidence, clinical or laboratory, of disturbance of the metabolic functions.

There was no untoward metabolic reaction either during or after surgery.

The prompt return of menstrual function after removal of the tumor was very gratifying. The loss of facial hair, while definite and progressive, is proceeding at a much slower rate and still, months after surgery, is incomplete.

The 17-ketosteroid output in case 1 showed values of 1.9 and 2.7 mg. per 24 hours. The normals are given by some as less than 1 mg. for infants. Determinations on normal infants in our laboratory have consistently run less than 0.3 mg. which would indicate an even greater disparity between the values obtained in this case and the normal. Unfortunately no determinations were made for the 11-oxy or corticoid group. Endocrinologists have believed that this 11-oxy group represents the fractions most responsible for the metabolic effects of the adrenal cortex while the 17-ketosteroids are responsible for the genital endocrine effects.

In case 2, the older girl, the 17-ketosteroids were enormously increased, with values of 88 and 90 mg. being obtained as against a normal of 8 to 12 mg. in 24 hours. The 11-oxy or corticoid level was 5.8 mg. for 24 hours before surgery as against a normal of 1 mg. Theoretically one would have expected more symptoms of metabolic upset than were actually present. We do not know how to explain this apparent discrepancy. Within a few weeks postoperatively the 17 ketosteroid levels were down to 16 mg. and the corticoids to 2.5 mg.

Several months after surgery the levels were 6.8 mg. total 17 ketosteroids and 2.0 mg. 11-oxy or corticoids. No determinations were made of the alpha and beta fractions.

It has been demonstrated that the number of eosinophiles in the circulating blood has an inverse relationship to the amount of adrenal cortical hormone present. The more hormone present, the lower the level of the eosinophiles. Thorn and his collaborators (J. A. M. A., **137**: 1005, July 17, 1948) have used this phenomenon as a test for the presence of adrenal cortical insufficiency. The exact reason for this relationship has not been entirely explained. However, that it occurs is well established.

Case 2 was followed for eosinophile counts[3] before, during and after surgery.

The normal level lies in the range between 100 and 250 eosinophils per cmm. of circulating blood. Before surgery the eosinophile level was within this normal range. At the time of surgery the count dropped rather sharply and then within 10 days after surgery rose to a high peak above the normal level. From this point there was gradual subsidence down to the level of normal or just a little below.

The explanation of the hematologists for this reaction is that there is some compensatory balancing mechanism in the body which compensated for the abnormally high level of adrenal cortical hormone which was constantly present before surgery. The fall below the normal level at the time of surgery, they attribute to a combination of an alarm reaction and the fact that adrenal cortical hormone was given intramuscularly at the time of surgery The high rebound after operation, they explain as being due to a preponderance of the compensatory mechanism, whatever it may be, after the release from the preoperative high hormone level Since removal of the tumor this has gradually readjusted back to practically a normal level It remains to be seen how much clinical importance this reaction will assume

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[3] These counts were made by Dr. J. A. Best of the Division of Hematology. Department of Medicine.

The gross and microscopic pathology of these tumors apparently has no specific relationship to the clinical picture Ponceau-Fuchsin stains were not done

SUMMARY

Two cases of tumor of the adrenal cortex are presented

One case, a female infant, presented obesity, edema, some slight genital hair growth and poor resistance to infection The child died of intercurrent disease before clinical proof of diagnosis could be made or surgical intervention done The diagnosis was confirmed at autopsy

The second case, a teen-age girl, presented a 2 year history of amenorrhea, hirsutism, acne, and hypertrophy of the clitoris The presence of a right adrenal tumor was confirmed by perirenal air insufflation, and surgical removal successfully accomplished with prompt and dramatic relief of the amenorrhea and amelioration of the other symptoms

Some interesting features of these cases are discussed

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RENAL CARBUNCLE (STAPHYLOCOCCAL ABSCESS OF KIDNEY)

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The clinical and pathological entity of renal carbuncle has been clearly established by numerous contributions on the subject, and therapy has been adequately covered from a surgical viewpoint. With the advent of the antibiotic drugs, a new impetus has been added to the conservative treatment of this type of kidney infection. This paper is a report on the use of penicillin in the treatment of a patient who, we believe, had a carbuncle of the kidney.

Pyogenic coccic infections of the renal cortex are mainly hematogenous and secondary to suppurative foci such as boils, carbuncles, abscesses, felons and infected wounds elsewhere in the body. Hugh Cabot[1] considered acute infections of the upper respiratory tract, particularly of the throat and nasopharynx, also of etiological importance as original foci. Nesbit[2] found that staphylococcus was present in 15 to 40 per cent of the reported cases of kidney infection. The age incidence ranged from 4 to 49 years, the average being 26. Sex incidence showed a 37 to 17 preponderance of the infection in males. Involvement of the right side was seen 31 times, and involvement of the left, 12; bilateral involvement occurred in 5 instances.

The actual frequency of kidney carbuncle is somewhat open to debate; however, McAllister and O'Conor,[3] after thorough investigation of the literature in 1932, accumulated 92 cases and added 2 others. Since that time they state that about one hundred additional cases have been reported. MacMyn[4] and others consider carbuncle of the kidney a condition which is still a comparative rarity. A review of the literature adds increasing importance to the term "comparative"; for it becomes obvious that, as diagnostic acumen and more efficient antibiotics are added to the armamentarium of the urologist, there will be fewer cases which will go to surgery for drainage as perinephric abscesses. Or, more ideally, the infectious process may be arrested in one of its earlier stages and the rarity of renal carbuncle may become an actuality.

Therapy, as noted in the literature to date, falls mainly into three classifications: 1) conservative treatment with minor import given to medications; 2) surgical intervention consisting of some form of drainage of the suppurating area either by puncture, incision or excision, enucleation, or decapsulation; 3) and nephrectomy for the more desperate cases.

With the advent of penicillin, streptomycin, and related antibiotic agents, a new approach has been fostered. McAllister and O'Conor[3] have published the first report in English on the use of penicillin to effect a spontaneous healing of the massive parenchymal infection.

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[1] Cabot, H.: Blood stream infections of the kidney. Brit. J. Urol., 8: 233–255, 1936.

[2] Nesbit, R. M.: Acute staphylococcal infections of the kidney. J. A. M. A., 98: 709–714, 1932.

[3] McAllister, R. W. and O'Conor, V. J.: The effect of penicillin in carbuncle of the kidney. Surg. Clinics N. A., 25: 210–218, 1945.

We wish to present our experience in the satisfactory use of this drug in a case with the thought that it may add some information and stimulus to published results in the use of penicillin and newer drugs in the treatment of renal carbuncle

Mr J H , a 20 year old colored man, was admitted to the medical service with the chief complaint of a persistent pain in the right flank of 1 week's duration, 10 days before admission, he had suffered an upper respiratory infection The pain was usually constant and worse at night when lying down Physical examination revealed a temperature of 102 F, tachycardia, limited excursion of right diaphragm, moderate right upper quadrant, flank and costovertebral angle tenderness, and no palpable mass The initial urine examination showed an acid urine with 30 to 40 white blood cells, no red blood cells, casts or bacteria Urine and blood culture offered no evidence of growth White cell count was 17,100 with 67 per cent polymorphonuclear leukocytes The nonprotein nitrogen was 34

The patient's temperature, ranging from 99 to 102 F, remained elevated for 3 weeks During the first 2 weeks, sulfadiazine was given in full dosage In the second week, a mass became palpable in the right upper quadrant Meanwhile, chest x-rays and Graham series were taken, and a retrograde pyelogram was suggested after an intravenous pyelogram showed abnormal findings Stool cultures were negative for the typhoid group

The patient was seen by the urological service on the seventeenth hospital day At this time additional physical findings were noted, namely, increased temperature of right flank, splinting of right flank muscles, percussion dullness over the right kidney, and a definitely palpable mass in the right flank

Retrograde pyelography, March 9 1948, showed free movement of the kidneys (inspiration and expiration, fig 1, *A*) and, as revealed in the intravenous pyelogram (fig 1, *B*), a filling defect of the superior major calyx with enlargement of the upper pole of the right kidney (fig 1, *C*) Indigo carmine appeared in 3½ minutes on the right and 3 minutes on the left The bladder urine contained no red blood cells and 5 to 10 white blood cells, the right ureteral specimen, 1 to 2 red blood cells and a rare white blood cell, and the left, only fresh (traumatic) red blood cells Urine culture grew Staphylococcus aureus from the right kidney specimen and bladder with a few colonies from the left (probable contamination)

Microscopic urinalyses throughout patient's hospital stay varied from no white blood cells to loaded and showed intermittent microscopic hematuria Blood cultures were negative In spite of the presence of bacteria by stained sediment, numerous urine cultures were negative with the exception of those previously mentioned White blood count varied from a high of 19,100 on admission to 8,800 at the time of discharge

Penicillin was ordered March 10 in doses of 100,000 u every 2 hours with sulfadiazine 0 5 gm 4 times a day, but for some reason, the written orders were not put into effect until March 13, the fourth day following cystoscopy On that day the temperature returned to normal and remained so Coincident with the sharp drop of the patient's temperature to normal, his urine again became loaded with leukocytes, the mass in his side disappeared, and he remained asymptomatic until his discharge on March 23 The penicillin and sulfadiazine were discontinued on March 21. Retrograde pyelogram taken *April 4*, *twenty-six days after initial studies*, showed normal filling of the previously obliterated superior major calyx (fig. 1, *C*). The urine at cystoscopy on April 4, after discharge from the hospital, contained a rare white blood cell; culture was deemed superfluous.

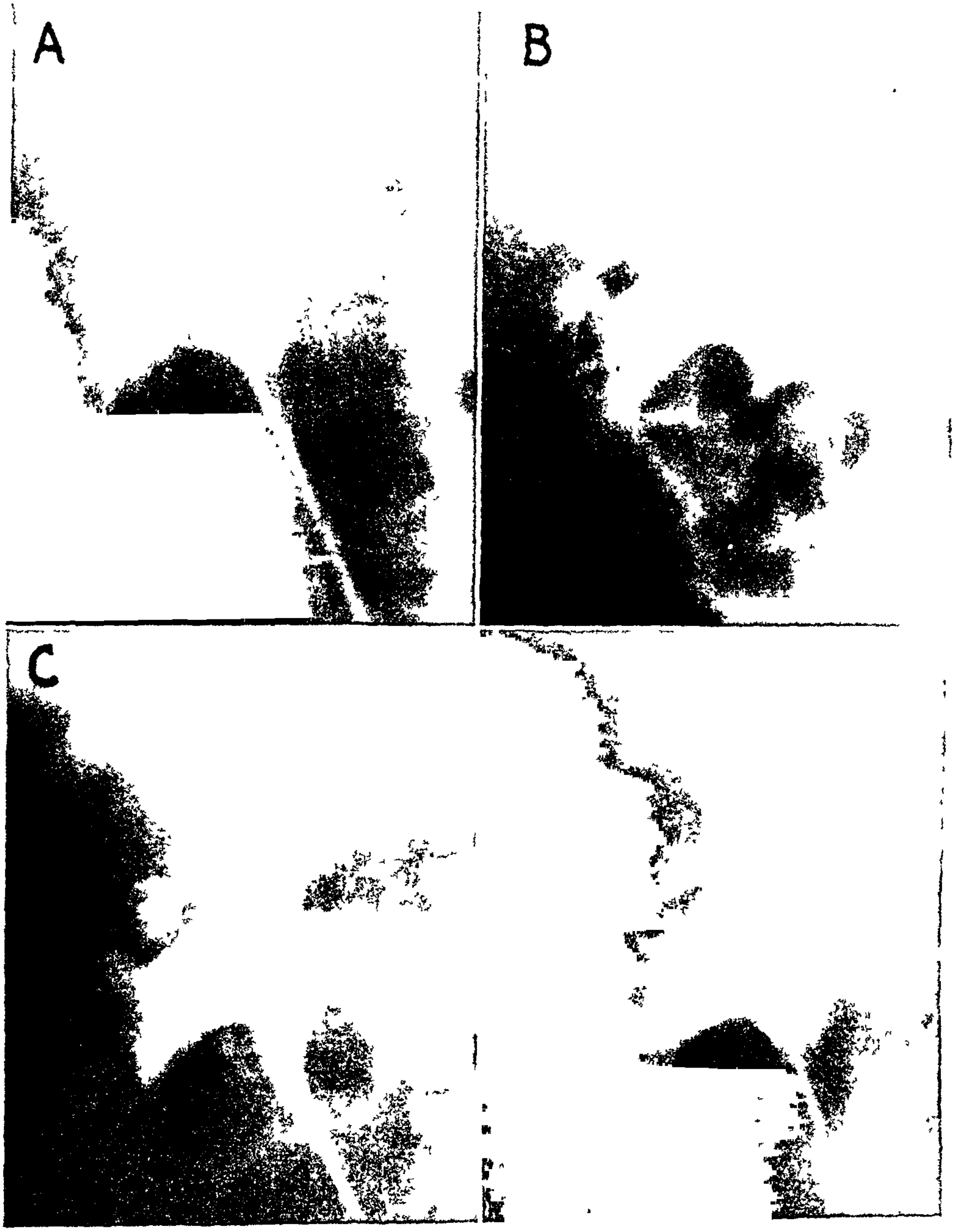

FIG. 1. *A*, retrograde pyelogram, double exposure (inspiration and expiration) shows free movement of kidney and ureter. *B*, intravenous pyelogram (15 minute film) shows filling defect of superior major calyx. *C*, retrograde pyelogram shows defect of superior major calyx as demonstrated by intravenous pyelography. *D*, retrograde pyelogram after recovery shows filling of superior major calyx.

COMMENT

Diagnosis in the above case naturally must be based on supposition in the absence of a biopsy, surgical or autopsy specimen We must therefore look to the positive findings

The roentgenological studies in the case were a definite factor in diagnosis and as a demonstration of recovery Many writers ascribe, at the most, a negative value to cystoscopy and pyelography Lazarus[5] Thomas and Exley[6] and MacMyn[4] are of this opinion, conversely, Cabot[1] and Nesbit[2] emphasize the value of pyelographic study Campbell[7] points out some of the diagnostic difficulties of pyelogram interpretation while Braasch[7] suggests that the exaggerated deformities in pyelograms in cases of perinephric abscess are due to concomitant alteration of the renal parenchyma itself, thus supporting the contention of Patch and Reid [8]

Urinary findings in suspected cases of renal carbuncle are often significant in the early stages of the disease for their normalcy, while minor urinary findings may be constant throughout Rupture into the renal pelvis will result in showers of pus cells and bacteria, often with, surprisingly, negative cultures This observation has been noted and is explained by Nesbit[2] through personal cummunications with Helmholz and Hadley as due to changes in the bacteria that render them sufficiently devitalized to fail to respond to the usual culture methods Stained smears and cultures are thus given a position of diagnostic importance and indicate the need of frequent, careful studies throughout the course of the disease as well as after recovery

Kidney function tests as an aid to the determination of the extent of kidney damage may be of little help as in the case presented in which indigo carmine was used Cabot and Crabtree[9] emphasized the value of the phenolsulphonphthalein test in differentiating between pyogenic and nonpyogenic group infections by stating 'Since the suppurative infections involve chiefly the cortex and comparatively little of the convoluted tubules, they would be expected to produce comparatively little effect upon kidney function thus measured, and such is in fact the case"

The role of sulfadiazine in the therapeutic treatment of our case is difficult to evaluate It is noted, however, that the patient's temperature remained elevated throughout the initial therapeutic dosage of the drug and that there was no perceptible change in clinical course or urinary studies Penicillin would have no doubt been given greater credit than it deserved had the original orders for therapy been carried out Significantly, the patient's temperature remained normal once penicillin therapy was instituted, and unlike McAllister and O'Conor's[3] case, complete asymptomatic recovery ensued Shearer, Wiper, and Miller[10] reported an excellent clinical result using penicillin lavage and intramuscular penicillin, 200,000 u. daily after surgical incision and drainage. It should also be noted that McAllister and O'Conor[3] used relatively small doses of penicillin, whereas our patient was given large doses. Finland[11] feels that in inaccessible in-infections, such as renal carbuncle, even though the organism is considered penicillin fast, massive doses at frequent intervals over a long period of time may often be found effective.

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[4] the kidney Brit J Urol , 4 11–19, 1932

[5] kidney, J Urol , 21 353-361, 1929

[6] Carbuncle of the kidney Minn Med 13 484–487, 1930

[7] Campbell, M F Renal carbuncle J A M A , 98 1729–1733, 1932

[8] Patch, F S and Reid, G Carbuncle of the kidney, etc Brit J Urol , 5 34–48, 1933

[9] Cabot, H and Crabtree, E G The etiology and pathology of non tuberculous renal infections Surg , Gynec & Obst , 23 495 536, 1916

[10] Shearer, T P , Wiper, T B , and Miller J M Renal carbuncle, etc J Urol 54 12 1945

CONCLUSIONS

A case of large presumable renal carbuncle is reported; recovery eventuates without surgical intervention.

The value of pyelography in diagnosis and follow-up is demonstrated.

The value of early diagnosis and conservative therapy is emphasized.

Urinary studies are of significant aid in following the course of the infection, both for negative as well as positive findings.

Blood and urine cultures may be negative though bacteria are present in urine smears and pyogenic kidney infections are considered hematogenous in their inception.

In the absence of the usual obvious sources of acute renal infection an obscure focus or upper respiratory infection must be considered.

Penicillin in massive doses may be of definite aid to recovery.

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[11] Finland, M.: Thorndike Service, Boston City Hospital. By personal communication with the authors.

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UNILATERAL CONGENITAL CYSTIC KIDNEY IN AN INFANT COMPLICATED BY HYDRONEPHROSIS

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Recently a case came under our care, an intra-abdominal cyst in a newborn, the exact nature of which was not evident to us until the pathological specimen was studied. Only one similar case can be found in the literature, that of Schwartz, which he termed "unilateral multicystic kidney in an infant."

M. D., a 10 day old female child, was admitted to Mercy Hospital from a foundling home, where, a few days after birth, she was observed to have a mass in the left flank, which gradually increased in size. The patient was a normal forceps delivery, and her general condition was good, she took her formula well. Physical examination revealed a well nourished child with a soft mass in the left flank, about 10 cm. in diameter, cystic in consistence. The hemoglobin was 9.0 gm., red blood count 3,280,000, white blood count 9,350. Routine urinalysis was negative. The nonprotein nitrogen was 25.7. X-Ray of the abdomen revealed a soft tissue mass in the abdomen, centrally and to the left, displacing the bowel to the right.

The clinical impressions were divided between those who thought that the mass was renal in origin, and those who felt that it represented a mesenteric cyst, although the latter opinion was most prevalent.

Because of the size of the mass and the uncertainty of the diagnosis, an exploratory laparotomy was advised. The infant, then 3 weeks old, was anesthetized with drop ether. A left rectus incision was made and there was exposed a multilocular cyst about the size of a large orange, lying presumably in the left side of the peritoneal cavity behind the transverse colon. No attachment to mesentery could be demonstrated, nor could the left kidney be palpated. The cyst was dissected away easily, no ligature being required in the process. It was the opinion at the operation that this was a mesenteric cyst. The incision was closed in the routine fashion, and the condition of the patient at the end of the operation being quite good. The duration of the operation was 19 minutes.

The baby gained in weight from 7 pounds, 8 ounces on admission to 9 pounds, 1 ounce on discharge 7 weeks later.

The gross specimen consisted of a large multiloculated cystic structure, measuring 12 by 9 by 7 cm. It was lobulated and contained about 25 cysts, the largest of which was 8 cm. in diameter, and the smallest, the size of a pin head. Many of the cysts intercommunicated, however, others could be dissected free of the rest of the specimen in toto without collapse. An atrophic ureter about 2 mm. in diameter was adherent to the kidney by fibrous connective tissue. To facilitate tracing its course to the renal pelvis, we injected a blue dye in the ureter. We found the ureter to turn completely upon itself about 2 cm. distal to the ureteropelvic junction so that it reversed its course for about 1 cm., and then it emerged into a "cyst" at a sharp right angle. The pelvis, which grossly was no different from the other cysts, was a thin-walled cyst, 6 cm. in diameter. This communicated with some of the other cysts by minute lumina and with the ureter by an opening about 1 mm. in diameter. Adjoining the atrophic ureter was a small nodule about 1 cm. in diameter, composed of rather firm reddish tissue, consistent with the appearance of renal tissue. The wall of the cystic structure was pale pink-yellow, smooth, dull and translucent, containing somewhat tenacious, thick colorless fluid.

Microscopic tissue sections of the kidney showed the walls of the cysts to be composed of several layers of fairly dense fibrous connective tissue. The lining consisted of a single layer of stretched out, extremely low cuboidal epithelium. The epithelium of the pelvis, while low, was taller than that of the cysts. The epithelium of the ureter was tallest of all; nevertheless it was still low cuboidal in character. The striking feature of the microscopic section was the presence of a few scattered glomeruli and tubules within the walls of the cysts. These structures were small but otherwise normal. Tissue section of the small nodule adjoining the ureter showed normal kidney tissue, comprising a few glomeruli and many collecting tubules.

An intravenous urogram showed that the left kidney was absent; the right kidney revealed moderately good concentrating capacity and appeared somewhat enlarged. There was no evidence of the presence of cysts in this kidney, although the urograms were not ideal.

Because of the apparent rarity of such a condition we were stimulated into inquiring into the subject of retroperitoneal and renal cysts. Polycystic kidney disease is usually a bilateral condition. Braasch has made the statement that polycystic kidneys are always bilateral in the adult. Cases described as unilateral frequently later develop the cystic process on the opposite side. It is the contention of some that if microscopic study of the alleged normal kidney in unilateral cystic kidneys is made, multiple cysts would be found which eluded the surgeon's hand. For this reason and for the reason that many of these cases later develop into bilateral polycystic kidneys, many of the reported cases of unilateral polycystic kidney have to be taken with a grain of salt.

Nevertheless in 88 autopsies of polycystic kidney disease, Ritchie found 2 to be unilateral. Nauman reported 2 unilateral cases among 16 cases of polycystic kidney disease. Bugbee and Wollstein reported 4 of 15 cases of unilateral polycystic kidney disease, one in an adult and one in a newborn child, and both corroborated by autopsy. Bell at the University of Minnesota reported 4 cases of unilateral polycystic kidney disease among 44 autopsies which revealed polycystic kidney disease. The unilateral cystic kidney differed in no way from the bilateral type. One patient was aged 6 months, one was a still born, one was 45 and one, 65 years of age.

Schwartz in 1936 reported a case of unilateral *multicystic kidney* in an infant aged 7 months. He used the term in contrast to polycystic kidney, for the typical polycystic kidney retains its general configuration and is studded with myriads of cysts separated by compressed islands of renal substance. The case reported by Schwartz contained much fewer cysts and very little kidney tissue between the existing cysts A laparotomy was performed, the pedicle was ligated and the left kidney removed Intravenous urograms had revealed a normal right kidney This is practically identical with the case being reported

A subject closely related clinically to the unilateral polycystic kidney is that of the retroperitoneal cysts, classified by Lahey and Eckerson in 1934 The most important group in their classification is the wolffian cyst or urogenital cyst The wolffian duct is the excretory mechanism in embryonic life for the pronephros and mesonephros and later develops to form the excretory apparatus for the male genital system With the formation and degeneration of 2 precursors to the final kidney (the metanephros), there is ample opportunity for cystic malformation among the tubules In fact it is surprising that we do not see more in the post embryonic life Lahey and Echerson report 2 cases, both in young adults, characterized by thin walled cysts, lined with cuboidal or columnar epithelium They were shelled out without difficulty, very few vessels required ligation They were not connected with any organs Other cases have been reported with only rudimentary kidney tissue in the cyst wall, which, in these latter, proves conclusively their origin These cases, which clinically might simulate the cystic kidney of our patient, differ significantly in two ways In these cases, the adult kidney on the same side as the cystic mass was present, and the renal tissue found among the cysts was rudimentary in nature and not of the metanephric type

As to the interpretation of this case we must admit much rests upon conjecture That this was not the usual example of polycystic kidney is indicated by the facts that it was unilateral as far as could be determined and that hydronephrosis complicated the original pathological process of cyst formation The pelvis, which was nothing more than a large cyst, communicated with the ureter by a very narrow opening The proximal portion of the ureter was very tortuous, evidently the cysts of the kidney, which arose as a maldevelopment of the metanephros during embryonic life, angulated the ureter to such an extent that the flow of urine was interfered with, thus resulting in the well known process of hydronephrosis Some of the cysts could be dissected away in their entirety from the rest of the kidney These then were not unlike the cysts of the polycystic kidney which, in theory at least, are found in the proximal portion of the renal system and do not communicate with the distal portion They do not contain urine Then, too, the epithelium of these independent cysts was not identical with the epithelium of the pelvis or ureter The former was considerably lower than the latter In the gross we have evidence that we were dealing with hydronephrosis inasmuch as the ureter was very tortuous and communicated with the dilated pelvis by a narrow opening Also in the gross we proved that we were dealing with a polycystic type of kidney disease since some of the cysts could be removed entirely from the rest of the specimen without loss of fluid Microscopically the epithelium of the cysts differed from that of the pelvis which grossly looked like the rest of the cysts Thus we have a case of foetal maldevelopment which per se interferes with the physiological functions of an organ, to the degree that it has become practically annihilated This is not merely an academic problem; the diagnosis of polycystic kidneys carries with it an ominous prognosis. However, with this type of unilateral congenital cystic kidney, the prognosis might be very favorable. The infant is 5 months of age at the present time. The genito-urinary system is functioning efficiently enough to permit the child to thrive.

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TRANSTHORACIC NEPHRECTOMY FOR METASTATIC OSTEOGENIC SARCOMA OF THE KIDNEY

DONALD F. MARSHALL AND EMERSON H. DRAKE

The purpose of this paper is twofold: 1) to re-emphasize the simplicity and advantages of the transthoracic approach for nephrectomy in selected cases; and 2) to report an unusual case of osteogenic sarcoma that metastasized to the kidney.

CASE REPORT

H. St. G., a white man, aged 23, appeared at the Maine General Hospital on February 16, 1938, complaining of pain, stiffness, and swelling of the right knee of 6 weeks' duration. Radiological examination revealed a bone-forming tumor of the lower end of the right femur (fig. 1). This was radiographically typical of an osteogenic sarcoma. A high thigh amputation was carried out. The diagnosis was confirmed on pathological examination (fig. 2, *A*). Radiological examination of the chest and pelvis at that time showed no evidence of metastases. The patient's postoperative course was uneventful, and he remained asymptomatic for the 10 years following.

In October 1948, the patient consulted his family physician because of a dull, aching pain in the left side, of 6 months' duration. There were no urinary symptoms. On the basis of the findings on x-ray in the abdomen and chest, he was re-admitted to the Maine General Hospital on October 24, 1948. Aside from his previous amputation, his past, family and social histories were irrelevant.

Physical examination demonstrated a sense of resistance in the left upper quadrant, but no definite mass was outlined, and neither kidney was palpable. The stump of the right femur was healthy and in good condition. The remainder of the physical examination was negative. X-ray studies showed a 4 cm. calcified nodule situated laterally in the left lung (fig. 3, *A*). A plain x-ray of the abdomen revealed a 9 cm. nodule of similar density in the region of the upper pole of the left kidney. Intravenous urograms showed a normal appearing right kidney, but no excretion from the left (fig. 3, *B*). The impression was that of metastatic involvement by osteogenic sarcoma of the left kidney and the left lung. Laboratory studies revealed a normal red blood count and hemoglobin value. The white blood count and differential were normal; blood urea nitrogen was 15 mg per cent, and bleeding and clotting times were normal. Urinalysis showed a *p*H of 5.5; sugar 0; albumin faint trace; microscopically there were numerous red blood cells, no bacteria. A preoperative diagnosis of metastatic osteogenic sarcoma of the left kidney and left lung was made.

On November 1, 1948, an operation was performed as follows: With the patient lying on his right side, an incision was made through the skin and muscles overlying the left tenth rib, and the rib resected subperiosteally from its angle to the costal cartillage. The chest cavity was entered, and a semicircular incision made through the diaphragm over the underlying kidney, which was displaced upward and outward by a tumor mass arising from its upper pole. After removing the spleen for greater exposure, the kidney pedicle was isolated with moderate difficulty, and the vessels ligated and divided individually. Following removal of the kidney, the diaphragm was closed with interrupted sutures of silk. A small posterior segment of the ninth rib was resected and the lingular portion of the left upper lobe was drawn into the wound. The tumor mass was amputated, the lung being whipped over with a running catgut suture. Three other small calci-

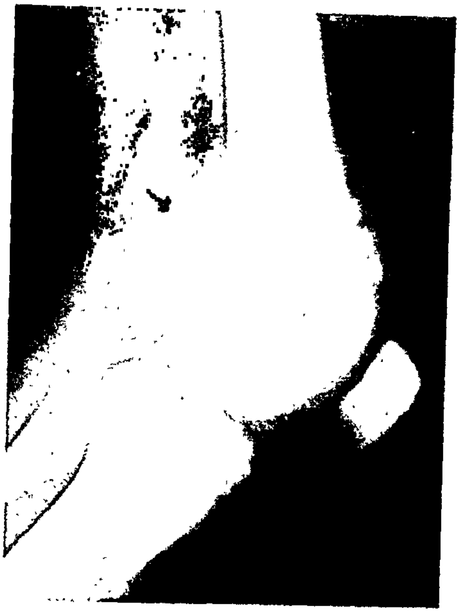
FIG. 1

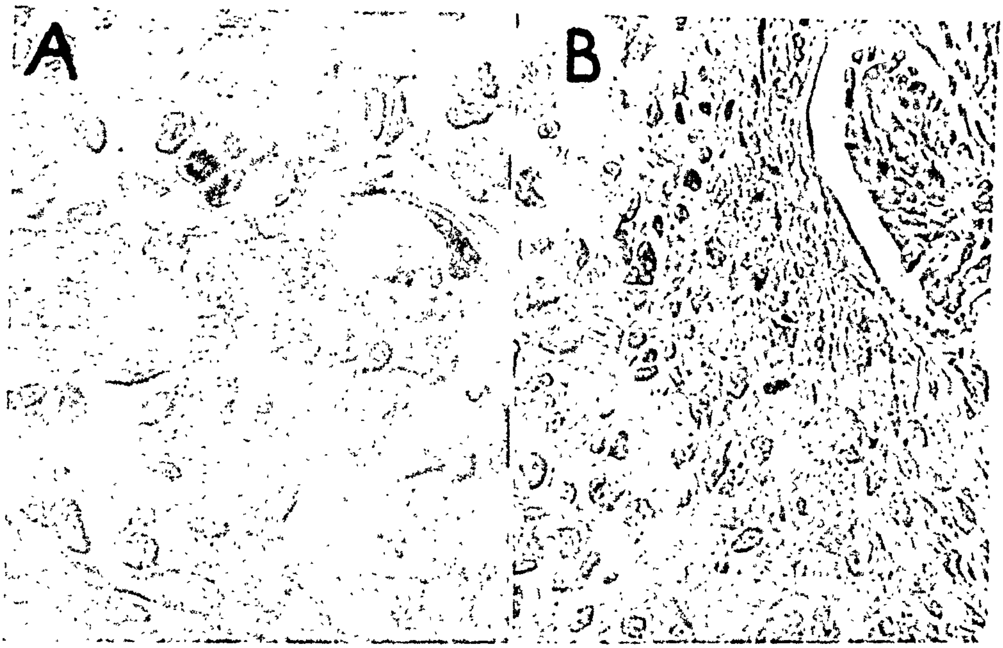

FIG. 2

fied pulmonary foci were palpated and removed individually, closing each defect with a small mattress suture. The chest wall was closed in layers with interrupted silk, with temporary intercostal drainage.

The postoperative course was entirely uneventful, and the patient was discharged home on his 14th postoperative day. Pathological examination (fig. 2, *B*) confirmed the diagnosis of osteogenic sarcoma with one large renal and one large pulmonary metastasis, as well as several smaller metastatic pulmonary implants.

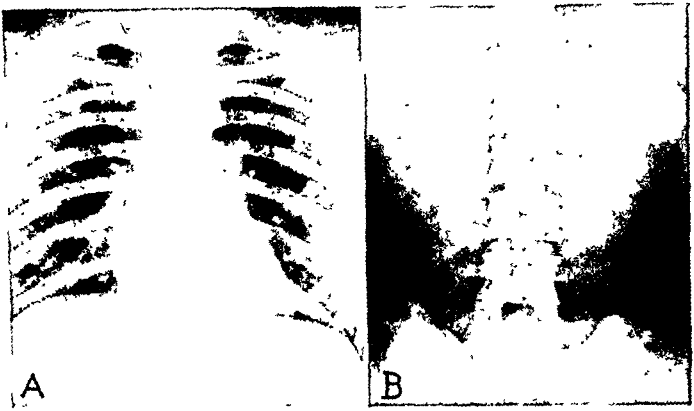

FIG 3

DISCUSSION

This patient was an ideal candidate for a transthoracic nephrectomy because the tumor was large and occupied the upper pole of the kidney. It was high under the costal margin, which would have made removal difficult by either the customary flank or the transperitoneal approach. In addition, the transthoracic approach made possible the examination of the left lung at operation.

Transthoracic nephrectomy was born of necessity in World War II. Six such operations were performed in 1944, during the Italian campaign, at the 8th Evacuation Hospital, affiliated with the University of Virginia. Details of this operation for traumatic thoraco-abdominal injuries have been described by one of us.[1] At that time it was felt that this operation would be feasible only on the left kidney because of the presence of the liver on the right side. However, since that time this operation has been employed independently by Dr. Richard Chute[2] and Dr. Wyland Leadbetter[3] for the resection of tumors of the right kidney as well. They have observed that in cases of large renal tumors the liver is displaced enough laterally to allow for the transthoracic approach.

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[1] Marshall, D F J Urol , 55: 119–132, 1946.

[2] Personal communication

[3] Personal communication

This approach is very convenient for the surgeon because of the excellent exposure of the renal vessels. In addition to this technique demonstrated at the 8th Evacuation Hospital in cases of traumatic thoraco-abdominal wounds, its advantages in nontraumatic selected cases have been demonstrated in a film by Dr. Richard Chute at the annual meeting of the American Urological Association in Boston, in May 1948. It is imperative that if this approach is used, an anesthetist well trained in endotracheal technique be available, and a thoracic surgeon makes a welcome member of the team. The unusually smooth convalescence of these patients is remarkable.

With the moderately encouraging results reported by Alexander and Haight,[4] from the resection of isolated pulmonary metastases of primary renal tumors, an occasional patient might lend himself to this means of resecting a solitary pulmonary nodule at the time of resection of the primary tumor, rather than at a later stage.

The recurrence of osteogenic sarcoma 10 years after resection of the primary lesion is unusually rare. The Army Institute of Pathology has a collection of approximately 150 osteogenic sarcomas, and according to Brig. Gen. R. O. Dart, USA, Director[5] "a considerable number" of these have developed metastases to the kidney. There is no record at the Army Institute of Pathology of primary osteogenic sarcoma arising in the kidney.

Hamer and Wishard[6] reported in July 1948, a case of primary osteogenic sarcoma involving the right kidney. These writers were able to find only two other cases of osteogenic sarcoma of the kidney.[7, 8]

Blades and Effler[9] reported, in February 1948, a review of the surgical treatment of the solitary lung metastasis.

The patient reported in this paper is being followed closely for evidence of recurrence. It seems highly unlikely that the resection of the pulmonary metastases in this particular individual will greatly prolong his life, but the extreme simplicity of this procedure with this approach led us to attempt to resect the gross tumors for whatever palliation possible.

ADDENDUM

The patient has been asymptomatic for 9 months. On August 22, 1949, he complained of swelling, with slight discomfort, in his left testicle. Examination showed an enlarged, firm left testicle, with one small area of stony hardness present. There was also a slight amount of fluid present, and some thickening of the spermatic cord.

A left orchidectomy was done on September 9, 1949. Pathological examination showed metastatic osteogenic sarcoma of the left testicle.

Metastatic tumors to the testicle, particularly of this type, are extremely rare.

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[4] Alexander, J. and Haight, C.: Surg., Gynec. & Obst., **85**: 129–146, 1947.
[5] Personal communication.
[6] Hamer, H. G. and Wishard, W. W., Jr.: J. Urol., **60**: 10–17, 1948.
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[8] Haining, R. B. and Poole, F. E.: Arch. Path., **21**: 44, 1936.
[9] Blades, B. and Effler, D.: J. Thoracic Surg., **17**: 27–37, 1948.

Radiographic examination of the chest showed no recurrence as yet in his lungs

SUMMARY

A diagnosis of metastatic osteogenic sarcoma of the kidney was made in a patient whose metastases occurred 10 years after the removal of the primary lesion in the right femur

A metastatic nodule was also identified preoperatively in the lingular portion of the left lung

The transthoracic approach was used to remove the kidney and a portion of the left lung

Transthoracic nephrectomy has proved to be a logical and simplified approach in selected cases

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POSTOPERATIVE STRICTURE AND PERIOSTITIS PUBIS FOLLOWING RETROPUBIC PROSTATECTOMY

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Retropubic, or extravesical suprapubic prostatectomy, was introduced into this country in 1947 by Millin, who told of excellent results and a remarkably short period of convalescence. This author in a subsequent monograph, based on an experience of over 375 cases, again emphasized the strikingly low incidence of postoperative complications. Later publications by Bacon and others apparently confirmed the value of the retropubic operation and stressed its desirability in most cases of major prostatic hypertrophy. The Gallic enthusiasm of Duvergey has prompted him to call this "the operation of the future." As a result of these reports, a considerable number of retropubic operations have now been done in the United States, and I believe that the time has come to evaluate our results.

This report is based on 33 retropubic prostatectomies which were done at our hospital by 5 surgeons, including residents. There was 1 death due to acute pulmonary edema (table 1). A moderate amount of bleeding was observed in 9 of our cases, but none of these required surgical measures other than blood transfusion. In contrast to intravesical suprapubic enucleation, these patients were quite comfortable after operation.

In this small series, however, we have encountered with appalling frequency two distressing complications:—postoperative stricture and periostitis pubis.

POSTOPERATIVE STRICTURE

Post-prostatectomy obstruction occurred 5 times in Millin's first 75 cases. Subsequently, the technique was so modified that either a wedge of the posterior lip of the bladder neck was excised or the bladder neck was sutured to the floor of the prostatic bed. Since Millin adopted this revised method, no further strictures occurred.

The technique followed by us at the Beth Israel Hospital was substantially the same as that described by Millin and Bacon, a V shaped wedge being excised from the posterior lip of the bladder neck in every instance. Despite this precaution, late stricture at the bladder neck was encountered in 9 of the 33 cases. Five responded favorably to urethral dilatation with bougies and sounds, two required secondary suprapubic cystostomy and internal urethrotomy, and the remaining two needed transurethral resection.

PERIOSTITIS PUBIS

Being well aware of the occasional occurrence of aseptic periostitis pubis, described by Beer in 1924, we were initially apprehensive that the wide exposure of the space of Retzius might predispose to this unpleasant complication. Therefore, special effort was made to avoid injury of the periostium of the pubis either by needle or by retractors.

Periostitis pubis occurred in 5 of our 32 cases. This painful condition incapacitated these patients from 4 to 8 weeks, and the course was apparently not influenced by any type of therapy. All eventually recovered (fig. 1). Our high incidence of periostitis pubis is in accord with the observations of Rosenberg and Vest, and also of Moore, though at complete divergence from the experience of Millin, who had never encountered this complication after a retropubic prostatectomy.

TABLE 1. *Retropubic prostatectomy: Complications*

Number of cases	33
Deaths	1
Stricture	9
Periostitis pubis	5
Postoperative bleeding	9
Femoral phlebothrombosis	2
Epididymitis	5
Pyelonephritis	1
Prostatic bed infection	
Incisional hernia...	

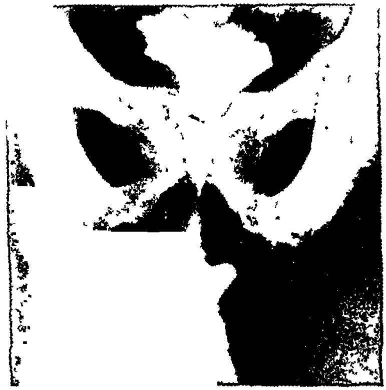

FIG. 1 Urethrocystogram, showing stricture at bladder neck. Note also periotitis pubis Beth Israel Hospital No 214666

SUMMARY

A high incidence of postoperative stricture at the bladder neck and of aseptic periostitis pubis has been observed in a series of 33 consecutive retropubic prostatectomies. These distressing complications constitute a serious deterrent to the routine application of the retropubic operation.

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DISTRIBUTION OF THE BLOOD VESSELS OF THE PROSTATE GLAND AND URINARY BLADDER: APPLICATION TO RETROPUBIC PROSTATECTOMY[1]

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A knowledge of the distribution of the blood vessels, particularly the veins, is imperative for the successful execution of any surgical operation. This is especially true of retropubic prostatectomy, in which a step of the operation is preliminary ligation of the veins on the anterior surface of the prostatic capsule.

Millin, who had done more than five hundred such operations and lauded the advantages of the procedure over other types of prostatectomy in suitable cases, first demonstrated his operation in this country at the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital in June 1947, at which time he stressed the fact that the vessels on the anterior surface of the prostatic capsule must be underrun and ligated before incising the capsule and removing the prostate gland. After operating upon several patients and noting the great variation in the configuration of the large veins at the prostatovesical junction, we decided to make a study of this region on cadavers inasmuch as such a study on a patient in the operating room could be limited only to the superficial veins which presented themselves during the course of the operation.

We dissected the pelves of several cadavers and discovered that the veins which are extremely thin walled were found in the layers of the endopelvic fascia. These veins have no valves. It was difficult to trace the course of the veins because only segments of them contained postmortem blood clots, which are a great help in dissecting blood vessels in that they are easily seen and felt. Dissection between segments of vessels containing blood clots was difficult because of the friability of the vessel walls. A collapsed vein or one without a contained blood clot was indistinguishable from its enveloping endopelvic fascia.

In reviewing the literature on this subject, we discovered that the principal studies, and the ones most frequently referred to, were those which were done by simple dissection of the postmortem specimen (Santorini, 1724). No accurate description of this group of veins and the plexuses was given. It was stated that a vascular plexus covered the anterior surface of the prostate and bladder. In a more recent article, entitled "The Function of the Vertebral Veins and their Role in the Spread of Metastases," Batson used "artist's tube water color" which was fluid and remained fluid, giving color to the tissues and at the same time being radio-opaque. By this means, he was able to follow the course of the material in the human cadaver and the anesthetized Rhesus moneky by fluoroscopy and roentgenograms. He also used latex rubber mass to fill the cranial veins and sinuses.

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[1] The actual dissected specimens from which the material for this paper was derived were exhibited at the annual meeting of the American Urological Association in Boston, Mass. May 17-20 1948.

MATERIALS AND METHODS

In dissecting our first two cadavers, the difficulty in following the course of the veins became apparent as we were never certain when vein or a portion of the endopelvic fascia was being followed. When colored fluid was injected into the vessels, some of the dye escaped through openings in the veins caused by dissection and thereby colored all the surrounding tissues and made further dissection futile. Distending the veins with colored solution before dissection was started allowed the veins to remain intact only so long as no dissection was carried out, for when dissection was done, a rent would invariably be made in a vein and the contained fluid would then be spilled and color the surrounding tissues.

✓ It occurred to us that the ideal solution for the successful execution of the study of these friable and collapsing vessels would be one which could be injected into the body of the cadaver in the fluid state at an elevated temperature, and which would solidify and form molded casts of the vessels when allowed to stand at room temperature. We found this ideal medium in a plastic substance which was not brittle and could form excellent casts. This substance, called Vinylite, consisted of two powders which were mixed together and thrown into solution by adding large quantities of acetone at a temperature above 70 C. Methylene blue was then added for coloring. This solution quickly began to crystallize when brought below this temperature.

The deep dorsal vein of the penis of three cadavers, whose ages were 63, 68, and 72 years respectively, were dissected and found to lie immediately under Buck's fascia. The superficial dorsal vein of the penis, which penetrates the suspensory ligament of the penis and the lower abdominal wall, was not used. The deep dorsal vein of the penis was then canulized and the freshly mixed and heated Vinylite solution was injected with gentle pressure. From 50 cc to 250 cc of the solution were used. The vessel was then tied off so that there would be no backflow, and the canula was removed. No further dissection was done. The cadavers were then placed in a refrigerator for 48 hours, after which they were removed and the anterior abdominal walls were excised.

The veins of the anterior abdominal wall were found to contain the blue plastic, as were many of the vessels of the thorax and head. The lower extremities were then disarticulated at the hip joint, and the large femoral and saphenous veins were found to contain plastic, as did the veins about the acetabulae. The obturator plexuses (both inner and outer) were completely filled and formed a beautiful outline. These vessels were filled despite the fact that the injection was made only into the deep dorsal vein of the penis. In dissecting away the gluteal muscles, the veins in these muscles and those in the lesser and greater sciatic notches were likewise found to be filled with the blue plastic. The hemorrhoidal veins were completely filled; and when the torso was sawed off at the first lumbar vertebra, the large vertebral vein at this point was completely filled.

The amputated pelves, which were separated from the abdomen and lower

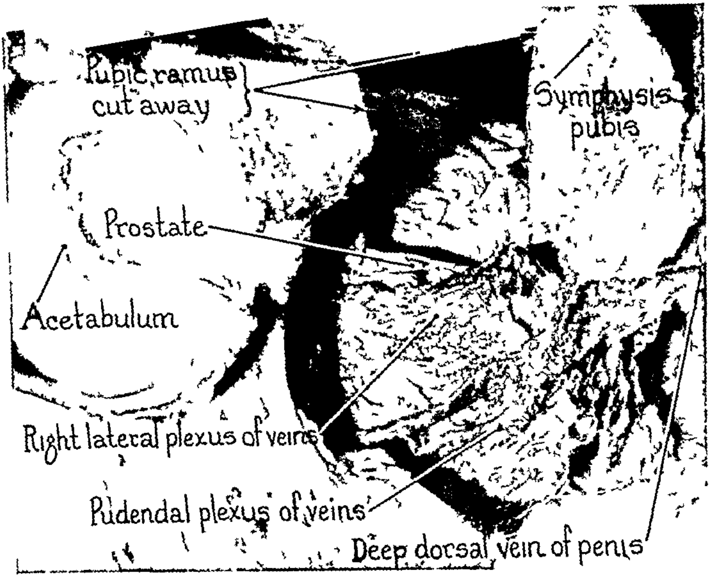

FIG 1 Photograph, showing formation of pudendal plexus and lateral prostatovesical plexus of veins Penis scrotum, gluteus and all other soft tissues have been cut away

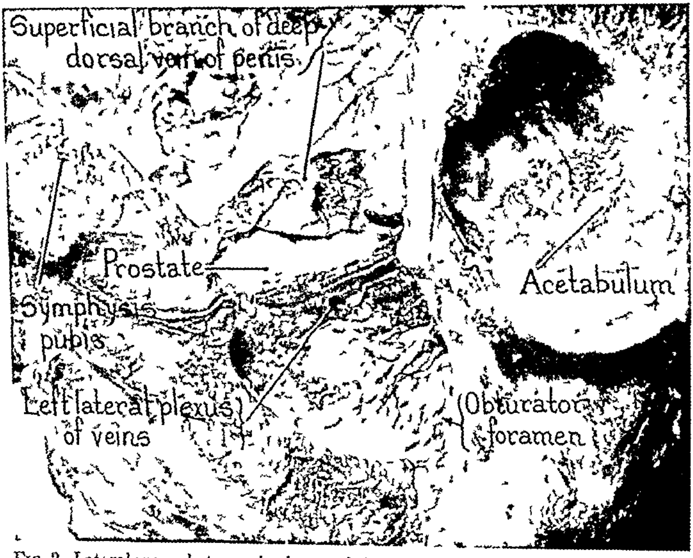
Superficial branch of deep dorsal vein of penis
Prostate
Symphysis pubis
Acetabulum
Left lateral plexus of veins
Obturator foramen

FIG 2 Lateral view photograph, showing left prostatovesical plexus seen through obturator foramen Vessel walls have been stripped off casts in some instances Part of obturator plexus can be seen on left and lower margins of obturator foramen Superficial branch of deep dorsal vein of penis (third branch) is seen coursing over lower anterior bladder wall

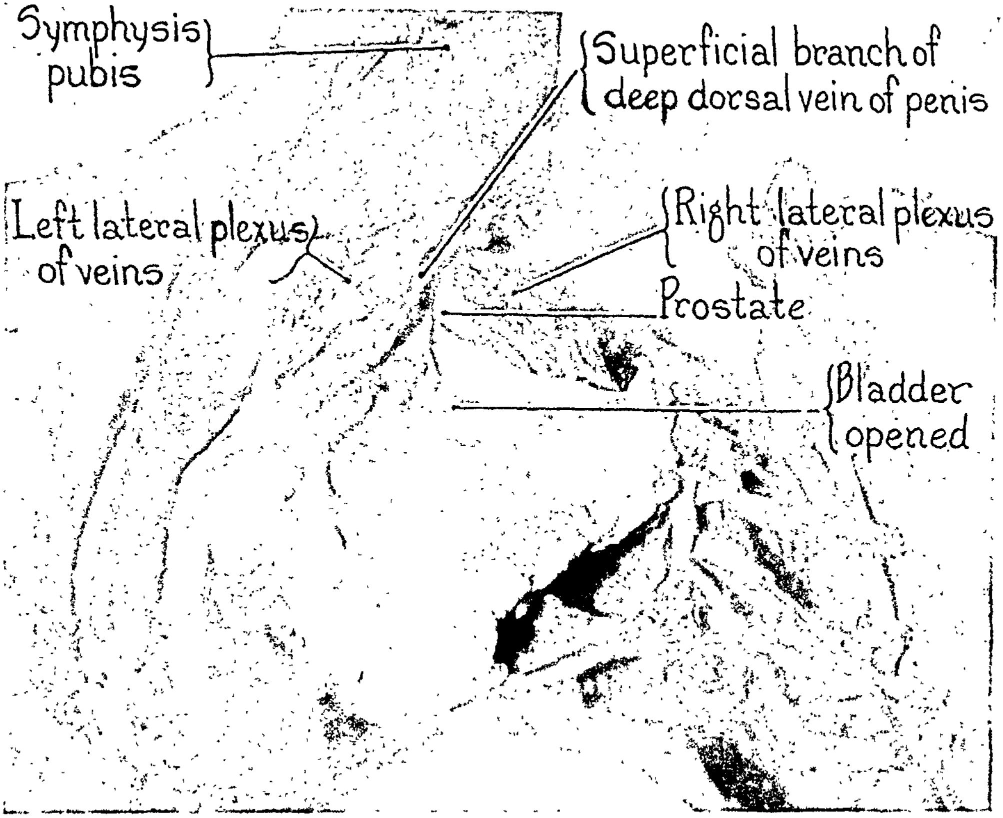
Symphysis pubis
Superficial branch of deep dorsal vein of penis
Left lateral plexus of veins
Right lateral plexus of veins
Prostate
Bladder opened

FIG. 3. Veins lying in endopelvic fascia on inner surface of pubic ramus and symphysis are seen in upper left. Large, prominent superficial branch of deep dorsal vein of penis is seen arising from main trunk at its bifurcation into right and left plexuses as it emerges from the triangular ligament. Bladder has been opened up to vesical outlet, thereby showing its proximity to branches of large vessels when prostate is small.

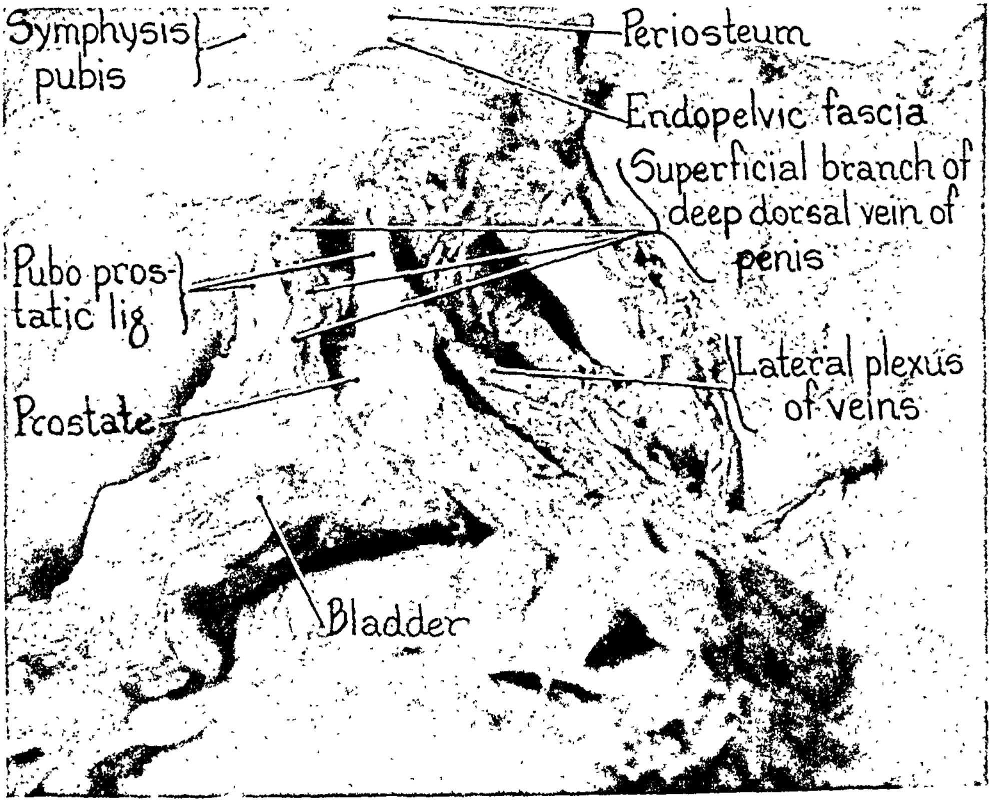

FIG. 4. Endopelvic fascia and vessels stripped off periosteum of symphysis pubis. Large, prominent, centrally located superficial branch of deep dorsal vein of penis is seen lying between two very well-developed puboprostatic ligaments.

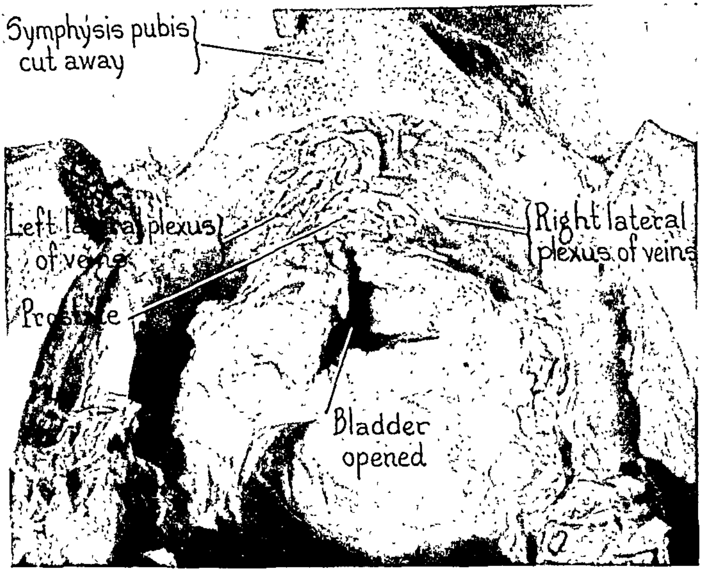

FIG. 5. Variation in configuration of group of veins on anterior aspect of prostate and bladder neck in this specimen of a 72-year-old male. Bladder has been opened up to bladder neck. Symphysis pubis has been cut away for better vision and photography.

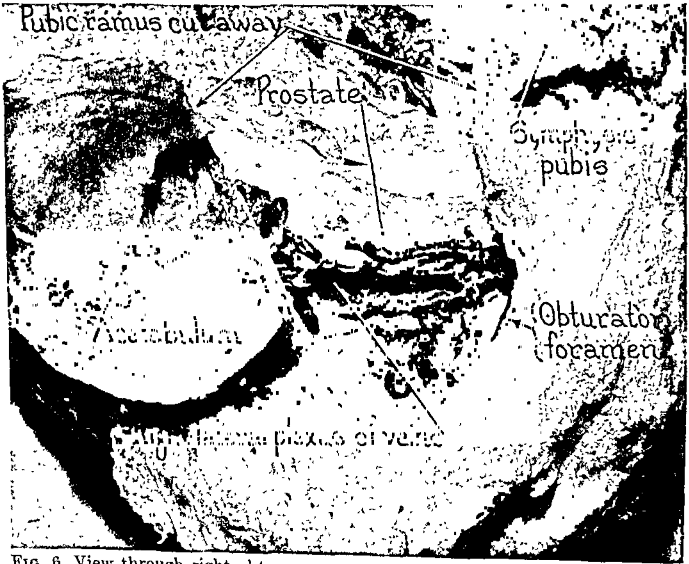

FIG. 6. View through right ateral prostatovesical
plexus of veins. Futility of sutu

limbs, were more manageable for detailed dissection. The retropubic fat and peritoneal contents had been removed. The veins over the symphysis pubis and

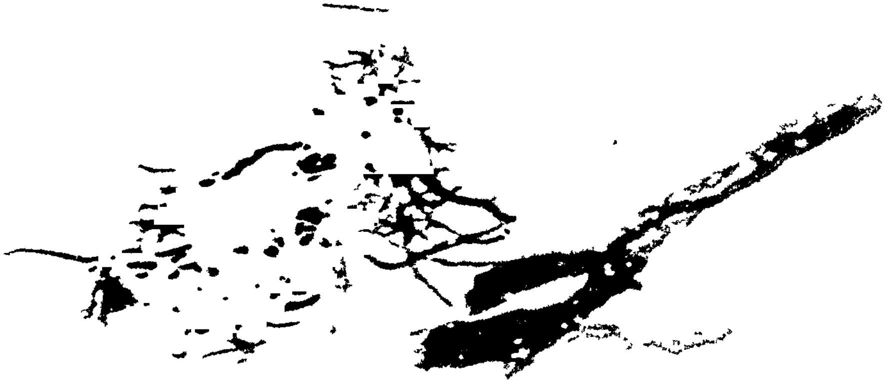

FIG. 7. Cast of entire venous circulation of stillborn male

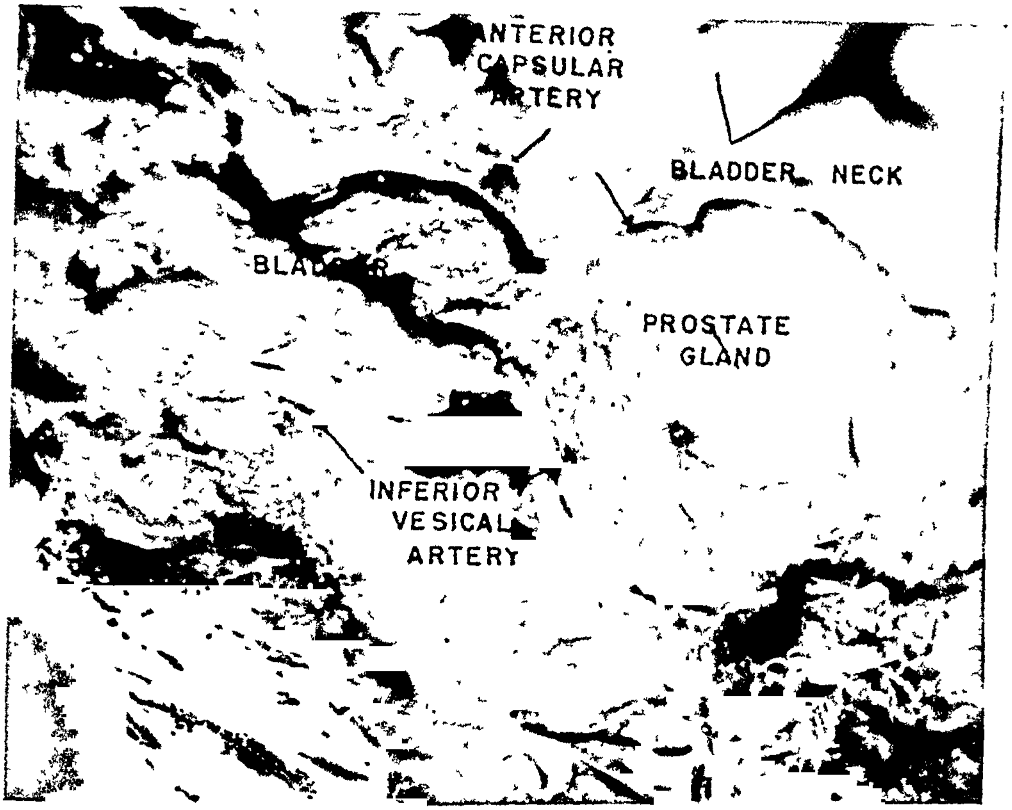

FIG 8. Arterial blood supply of prostate and bladder neck. View from right side.

pubic rami were dissected and found to lie in the endopelvic fascia over the periosteum. The configuration of these vessels varied in each case. These vessels were branches of the lateral plexus of veins about the prostate. When the ramus of the pubis and the ramus of the ischium were cut away (fig. 1), and the entire penis and scrotum were cut away except for the deep dorsal vein of the penis, the plexus of veins was clearly seen. The deep dorsal vein of the penis penetrated the triangular ligament (urogenital diaphragm) to contribute the major share in the

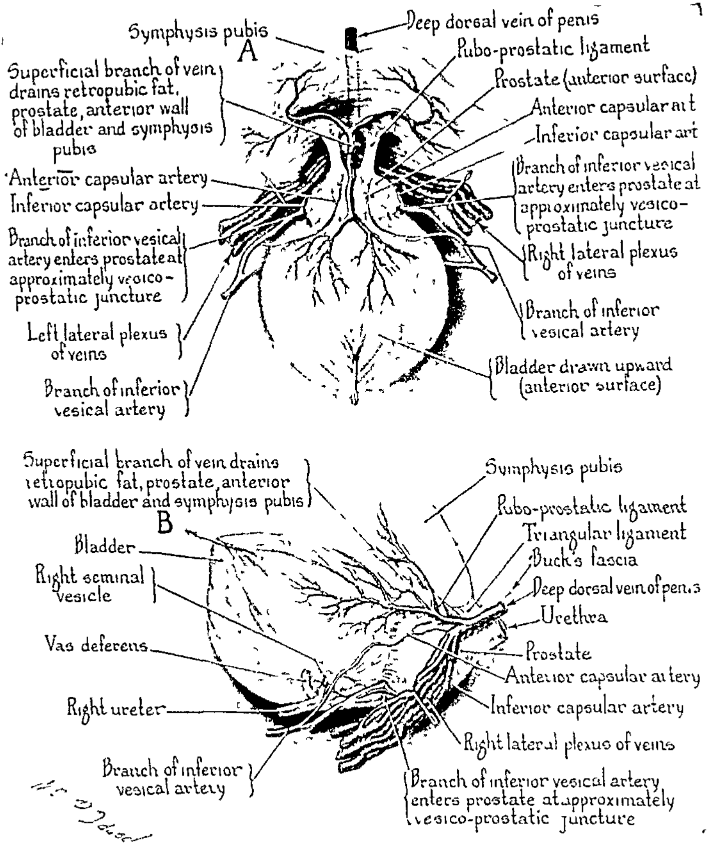
A
Symphysis pubis
Deep dorsal vein of penis
Pubo-prostatic ligament
Superficial branch of vein drains retropubic fat, prostate, anterior wall of bladder and symphysis pubis
Prostate (anterior surface)
Anterior capsular art
Inferior capsular art
Anterior capsular artery
Inferior capsular artery
Branch of inferior vesical artery enters prostate at approximately vesico-prostatic juncture
Branch of inferior vesical artery enters prostate at approximately vesico-prostatic juncture
Right lateral plexus of veins
Left lateral plexus of veins
Branch of inferior vesical artery
Branch of inferior vesical artery
Bladder drawn upward (anterior surface)
B
Superficial branch of vein drains retropubic fat, prostate, anterior wall of bladder and symphysis pubis
Symphysis pubis
Pubo-prostatic ligament
Triangular ligament
Buck's fascia
Deep dorsal vein of penis
Urethra
Bladder
Right seminal vesicle
Prostate
Vas deferens
Anterior capsular artery
Inferior capsular artery
Right ureter
Right lateral plexus of veins
Branch of inferior vesical artery
Branch of inferior vesical artery enters prostate at approximately vesico-prostatic juncture

Fig 9. Composite illustrations from injected specimens, showing arterial and venous circulation of prostate, bladder and retropubic area *A*, anterior view, *B*, lateral view.

formation of the lateral prostatovesical plexus, the pudendal plexus, and the obturator plexus of veins. The last plexus consists of two rings of veins, one overlying the other, surrounding the margin of the obturator foramen. It sends a branch into the lateral prostatovesical plexus. In figure 2, where the bone is not cleared of all venous tissue, remnants of the obturator plexus can be seen on the left margin of the obturator foramen.

As the deep dorsal vein of the penis emerges from the triangular ligament, it gives off three branches, namely, a right, a left, and a superficial or central branch. The last branch is clearly seen in figure 3. This is the large vein which first confronts the surgeon when clearing the retropubic area to obtain exposure of the prostatovesical junction. It is easily accessible for ligature and can sometimes be retracted from the field of operation. Figure 3 shows several large veins coursing on the inner surface of the pubic ramus and symphysis pubis over the periosteum and lying in the endopelvic fascia. The endopelvic fascia and veins are dissected off the symphysis in figure 4. The central position of the superficial branch of the deep dorsal vein of the penis is clearly shown by its relation to the well-developed puboprostatic ligaments of this specimen.

With the symphysis pubis cut away, the variation in the configuration of the vessels forming the prostatovesical plexus is seen in figure 5, which was the specimen of a 72 year-old male. Although this specimen had the largest prostate gland of the group, it was not pathologically large.

The lateral plexus of veins assumes added importance when a transverse capsular incision is extended laterally in delivering a large prostate gland. In such cases, these veins may be opened and profuse bleeding will follow. The futility of suture ligatures here can be made apparent by observing the plexuses in figures 1, 2, and 6, while in figure 5 the plexus is less dense and may be amenable to suture ligatures for the control of bleeding. This same situation is met with during removal of the urinary bladder. In dissecting out the vessels of the lateral plexus, it was found that the walls of the vessels were very thin and in many instances were easily stripped away from the plastic contents (fig. 6). Because of this danger of damage to vessel walls in this area, Beneventi and Twinem have not advocated the placing of gauze sponges as traps for spilled blood in the lateral prostatovesical recesses during the course of retropubic prostatectomy. The proximity of the confluens of the right and left lateral plexuses to the vesical neck in patients with small prostates can be noted in figure 3. Aside from the fact that small prostates are more accessibly removed by the transurethral method, this is another good reason for not doing a prostatectomy by the retropubic route when the obstructing gland is small.

A small cast of the entire venous circulation in the stillborn male was made by injecting the blue plastic into the abdominal vena cava. The entire body, except for the plastic cast of this venous architecture, was then macerated in fuming nitric acid. The case was then set in an encasement of transparent plastic material (fig. 7).

ARTERIES

Vinylite plastic, colored red in fluid form at 70 C, was injected into the internal iliac artery of a 44 year old male cadaver and allowed to set. The moderate-sized inferior vesical arteries were seen penetrating the prostate at the prostatovesical junction and giving off an anterior capsular branch which lay on the anterior surface of the prostate (figs. 8 and 9).

We wish to express our appreciation to Dr. Oswald S. Lowsley, Director of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital, for his encouragement; to Mr. William P. Didusch, of Baltimore, Maryland, for his invaluable suggestions and meticulous illustrations; and to Mr. Percy Brooks, of the Photographic Department of the New York Hospital, for his fine cooperation and photographs. Our reliance upon these collaborators was necessarily great as photographs and illustrations were made as the dissection progressed.

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INTERSTITIAL CELL TUMORS OF TESTIS

REVIEW OF LITERATURE AND REPORT OF CASE; DISCUSSION OF GYNECOMASTIA AND TESTOSTERONE; INCIDENCE IN ANIMALS AND EXPERIMENTAL PRODUCTION OF INTERSTITIAL CELL TUMORS

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Tumors of the interstitial cells of the testis are rare but interesting because of the pronounced endocrine disorder that they can induce. The case we report is the first in 294,509 admissions to the Columbia-Presbyterian Medical Center of New York over a period of 19 years.

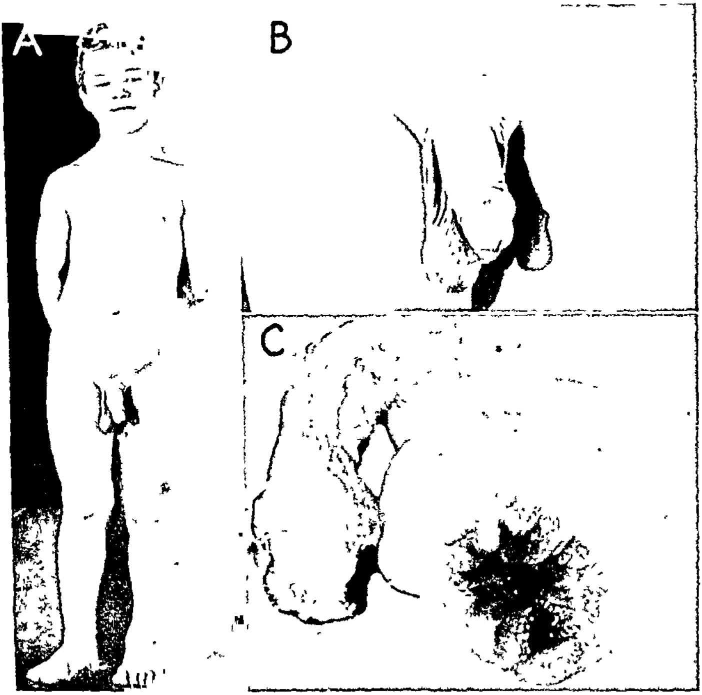
CASE REPORT

W. J. (No. 845812), aged 5, was admitted October 19, 1946. The child had developed normally until about 6 or 8 months ago, at which time it was observed that his genitalia were growing rapidly, the pubic hair increasing, and the voice deepening. About 5 months prior to admission, he began to have erections. He had always been large for his age. Three months ago, the family physician suggested a study of the endocrine system.

Physical examination: Temperature 98.6 F; pulse 104; respirations 20; blood pressure 110/70; weight 31,550 gm.; height 126 cm. The patient was a well-developed boy (fig. 1, *A*) who appeared to be considerably older than his stated age and who spoke with a deep adult male voice. Kinky pubic hair was present, and the penis and scrotum were of adult size (fig. 1 *B*). A large right testis, which did not transilluminate, was present in the right side of the scrotum. It was slightly irregular and hard. Rectal examination revealed a prostate which was approximately the size of one in an 18 year old boy.

Urine: pH 5.5; specific gravity 1.022; negative. Prostatic secretion: white blood cells 3–4 per high power field; red blood cells 6–8 per high power field; occasional epithelial cells; no spermatozoa. Hemoglobin: 13.5 gm.; red blood cells 4,720,000; white blood cells 10,300; polymorphonuclears 59; lymphocytes 28; monocytes 8; eosinophiles 5. Blood chemistry: calcium 10.7; protein 6.2; alkaline phosphate 16.5; acid phosphate 2.8; albumin 4.78; globulin 2.32; total proteins 7.10; sugar 97; nonprotein nitrogen 27.8; urea ratio 36.4. Urine 17-ketosteroids 1) 7.4 mg./24 hours, 2) 10 mg./24 hours (normal for 5 years, 7–8 mg.). Creatinine excretion 180 mg./24 hours. Creatinine retention test—1150 mg. exogenous creatinine given after 48 hours of creatinine-free diet, 28 per cent excreted in 48 hours (unchanged). This is the type of creatinine metabolism seen in post-pubertal males. Tuberculin test negative. Nose and throat culture—pneumococci, group II. Friedman reaction negative. Repeated Kline and Wassermann tests ranged from negative to 4+ (Kline test taken on father and mother negative). Basal metabolism +7.5 per cent. Intelligence quotient 106. Voice recording made.

X-rays of the long bones showed that the skeletal age was that of an adolescent and approximated the average for a male of 12–13 years. Skull (*frontal and lateral projection*), no abnormalities visible. Dental x-rays were approximately normal. No abnormalities were visible in the chest or abdomen. The kidney shadows were normal; no evidence of calculi. Intravenous urography showed normal filling and emptying of both kidneys. There was no real evidence of an enlarged adrenal gland.



[illegible] of patient. Note macrogenitosomia *B*, genitalia, showing right [illegible] eft because of tumor within it *C*, gross specimen after sectioning. Note large, [illegible] dark area.

Operation: Right orchidectomy by Drs. Ivers and Robinson on October 29, 1946. The postoperative course was uneventful.

Pathological report, No. 7410 (Dr. M. M. Melicow): The gross specimen was a right testis containing a central brownish tumor. (fig. 1, *C*).

Microscopic sections (fig. 2) revealed the picture characteristic of an interstitial cell tumor. The cells were large and arranged in masses, at times in intertwining broad cords. Branching connective tissue septae separated groups of cells and a band of fibrous tissue separated the tumor from the neighboring compressed testicular tissue. The cells were oval or polygonal and possessed eccentric, large, round nuclei with prominent nucleoli. The cytoplasm was granular and more dense in some fields than in others. No crystalloids could be identified. There was no change suggestive of malignancy.

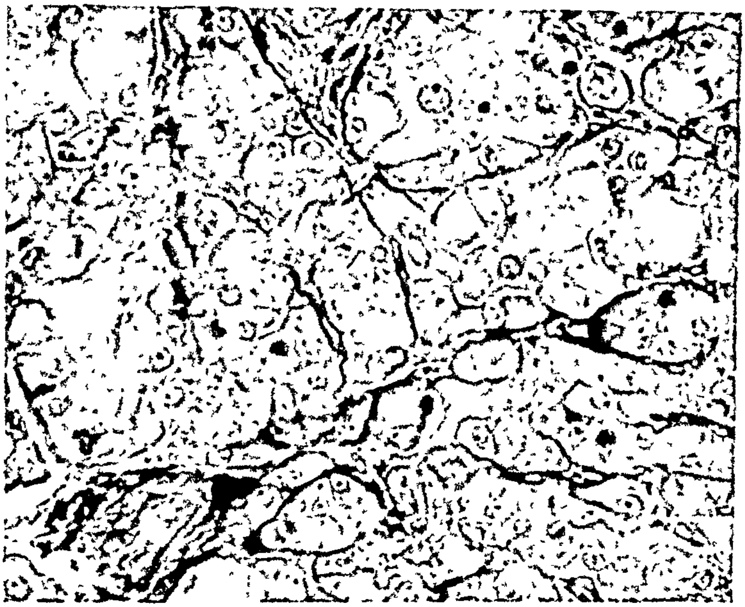


FIG. 2. Photomicrograph of interstitial cell tumor showing collections of large pale cells with eccentric nuclei and prominent nucleoli.

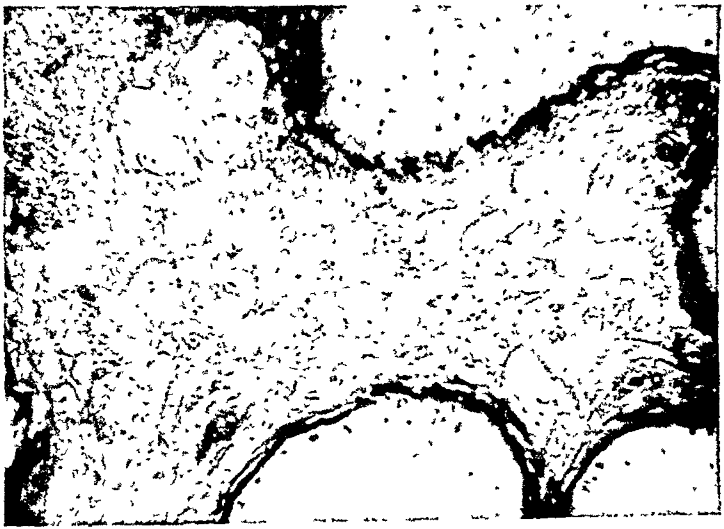


FIG. 3. Trichrome stain of masses of interstitial cells between tubules.

While spermatogenesis was not seen, there nevertheless was considerable activity of the spermatogonia.

The findings were compatible with a diagnosis of a tumor of the interstitial cells of the testis. It was apparently a benign neoplasm. The clinical picture, i.e., accelerated puberty in a 5 year old boy, could be explained by the pathologic findings.

Diagnosis Tumor of interstitial cells of testis (interstitioma of testis)

The patient was discharged November 18, 1946

Follow-up January 21, 1947, the voice remained the same, general condition good March 18, 1947, penis 8 cm in length, 9 cm in circumference, left testicle normal in size, no palpable lymph nodes, prostate about size of normal 18 year old, voice unchanged, Kline test 3+, alcohol and cholesterin antigens negative

The patient was re-admitted to the hospital on April 15, 1947 There had been no change in the voice or in the external genitalia He had chicken pox 1 month ago

Physical examination Temperature 99 8 F, pulse 100, respirations 20, blood pressure 112/68, weight 32,300 gm, height 130 cm, head 50 cm, chest 65 cm, abdomen 61 cm The boy appeared short, stocky, big-boned and much older than his stated age of 5½ years He was co operative and answered questions in a deep hoarse voice A moderate amount of curly pubic hair was present The penis was large and circumcised, and measured 2 cm in circumference and 8 cm from base of the shaft to tip of the glans when dependent, and 9 cm in circumference and 8 5 cm in length when erect The right testicle was absent The left measured 3 by 2 by 1 5 cm The prostate was easily palpable The extremities were muscular and the bony structure heavy His hands and feet were wide

X-rays of the kidneys, ureters and bladder were negative The chest was negative The hands and wrists showed increased maturation, the skeletal age was 13 years, 9 months X rays of the long bones showed a distinct increase in their length, and maturation was present The pelvis showed maturation, but not so marked as in the long bones Impression Progressive advancement in maturation in past 6 months in spite of removal of interstitial cell tumor

Laboratory report Hemoglobin 12 0 gm, red blood cells 4,200,000, white blood cells 5,100, platelets normal, polymorphonuclears 62, lymphocytes 36, monocytes 2 Urine *p*H 6 0, specific gravity 1 020, microscopically negative Tuberculin test negative Kline negative Urine 17 ketosteroids· 2 2 mg /24 hours and 3 8 mg /24 hours

The boy was discharged April 23, 1947 He was seen on May 6, 1947 No further change was noted

HISTORY

It is almost a century (1850) since Leydig described the interstitial cells of the testis, and a little over 50 years (1895) since Sacchi published what was probably the first report of a tumor of this type associated with macrogenitosomia The patient was a 9 year old boy who "looked like 18" and in whom the stigmata of precocious puberty started when he was 5½ years of age The voice became deep, a mustache appeared, and a beard appeared which grew to 5 cm in length He had pubic hair, his penis was large (9 cm long and 9 cm in circumference), and erections were frequent Some regression occurred after removal of the left testis which weighed 289 gm and which contained a large brownish mass One month after operation, the arm and leg hairs fell out, the voice was no longer adult male, and 4 months later the beard disappeared but the mustache persisted

No further changes were noted 10 months after operation. Sacchi had diagnosed the condition as coccidiosis, but the review warrants a diagnosis of a tumor of the interstitial cells. Chevassu, in 1906, identified such a neoplasm in the testis of a 27 year old man, but the case was not associated with any demonstrable endocrine disturbance. The first to recognize and report an interstitial cell tumor of the testis in a boy (age 9) with precocious puberty were Rowlands and Nicholson (1929). Like Sacchi's case, their patient too "looked like 18," but unlike it he showed no regression following removal of the benign neoplasm.

These reports, plus the more recent ones (table 2) constitute the total number, ten, of known cases to date. It is surprising that so small a number of interstitial cell tumors have been reported. Recognizable dyscrasias of other endocrine glands are apparently far more common than those of the interstitial cells of the testis. Why are disturbances of the interstitial cell so rare? Are they more common but not discernible, especially in adults? We have as yet no definite means by which one can histologically appraise the degree of function in the interstitial cell. What constitutes the normal number of islets for any age group, what determines hyperplasia, neoplasia benign or malignant (except in cases with metastases), is at times not clearly defined. One might expect histological evidence of interstitial cell overactivity in cancer of the prostate gland. Studies do not reveal any significant alteration in interstitial cell content of testes that had been removed in such cases. Teem found no relation between disease of the prostate (benign or malignant) and the number of interstitial cells (504 cases). One of us (Melicow) has examined sections of testes removed from over 150 cases of cancer of the prostate, and found that the majority showed no significant alteration in the interstitial cell content, some showed fewer than average, and a few revealed moderate hyperplasia.

Our knowledge of disturbances associated with tumors of the interstitial cell is meager because case reports are few. It is desirable, therefore, to present a résumé of accrued information regarding these cells, a summary of the reports of cases of hyperplasia and of tumor in human and animal testes, and of reports on the experimental production of such tumors.

THE INTERSTITIAL CELL OF THE TESTIS

The "normal" interstitial cell is usually large (14–21 μ) (Shields), spheroidal or oval, and contains a small round eccentric pale nucleus (sometimes red and wrinkled with one or two nucleoli). Binucleate and multinucleate cells are not uncommon and have been reported by Leydig, Von Winiwarter, Rasmussen, Maximow, Cowdey, Oberndorfer, Wiender, and Stieve. Nelson studied 721 testes from 470 autopsies (18 years and over) and in 85 testes found giant interstitial cells with 4–30 nuclei (usually 8–10). The cytoplasm contains inclusions: refractile granules, brownish granules (lipofuchsin) and at times rod-shaped crystalloids with rounded or pointed ends (Reinke's crystalloids). The interstitial cells usually occur in groups of 4 or 5. Arey states that these cells are transformed from the mesenchymal stroma between seminiferous tubules and are therefore of connective tissue origin. Stieve and Huffman are of similar opinion. Kaufmann

TABLE 1 *Cases of interstitial cell hyperplasia*

AUTHOR	YEAR	AGE	AUT OR OPER	LOCATION	HISTOLOGY	REMARKS
Stroebe	1897	63	Autopsy	Bilat	In groups between tubules	+ uterus
Pick	1905	38			In groups between tubules	
Dürck	1907	25	Autopsy	Bilat	In sheets between tubules	
Dürck	1907	64	Autopsy	Bilat	In sheets between tubules	Abdominal testis
Dürck	1907	45	Autopsy	Bilat	In sheets between tubules	
Dürck	1907	43	Autopsy	Right (?)	Seminiferous tubules destroyed	Left testis destroyed, blow to scrotum 1 yr prior
Koch	1910	56 64 6		? ? ?	Nodular hyperplasia	Age 6, lues
Orsós	1931	44	Operation	Bilat	In sheets between tubules	Hernia, uterus and adnexa
Grynfeltt *et al*	1933	56	Operation	Unil	In cords between tubules	Testis 2 cm above uterus
Le Chuiton *et al*	1935	13	Autopsy	Unil		+ seminoma
Cleghorn *et al*	1938	23	Autopsy	Bilat	Tubular atrophy	Pinealoma also present
Snellman	1939	67	Operation	Right	Brown patches Interstitial cell masses Aspermogenesis	Opposite testis normal
Warren and Olshausen	1942	46	Operation		In sheets between tubules	X ray exposure (?)
Warren and Olshausen	1942	46	Operation	Bilat	Reddish brown	Opposite testis removed 3 mo after 1st operation
Melicow	1947	21	Operation	Right	In sheets between atrophic tubules (fig 3)	At 4 years, herniotomy and right orchidopexy which, however, remained in inguinal region Right orchidectomy at 21

TABLE 2. *Interstitial cell tumors in children*

AUTHOR	YEAR	AGE OF ONSET	AGE WHEN FIRST SEEN	APPEARANCE	HEIGHT	VOICE
(1) Sacchi	1895	5½	9	"Looked like 18"		Adult male
(2) Rowlands and Nicholson	1929	6	9	"Looked like 18"	60″	Adult male at 7
(3) Stewart, Bell and Roehlke (fig. 5)	1936	4	5		51″	Low
(4) Somerford (fig. 6)	1941	5	11	"Looked like 18"; acne		Adult male
(5) Huffman	1941	4 Kicked in left testis	6	Enlarged breasts. Growth of genitalia	51″	
(6) Masson	1941	4	9 yrs., 7 mo.	"Looked like 18 or 19"		Adult male
(7) Werner (fig. 7, *C*)	1942	5	6	Precocious sex and body development		Adult male
(8) Rezek (fig. 7, *A* and *B*	1943 (seen)		10	"Looked like 18" Heavy-muscled	Tall	Adult male
(9) Anderson, W. D. A. Contributor (Accession 115779. Atlas of GU Pathology, Army Inst. of Path., P. 170, (N. B. Friedman & J. E. Ash))	1946		6	Deep, heavily muscled, adult configuration. Smoked cigars	Tall	
(10) Melicow *et al.* (fig. 1, *A* and *B*)	1947	5	5½	Precocious sexual development	126 cm.	Adult male

TABLE 2—*Continued*

AUTHOR	HAIR DISTRIBUTION				PENIS	ERECTIONS	SIDE INVOLVED	OPERATION
	Chin	Chest	Axil.	Pubic				
(1)	+	–	–	+	9 cm. long., 9 cm. circumference	Frequent	Left	Orchidectomy
(2)	–	+	–	+	Not mentioned	Not mentioned	Left	Orchidectomy
(3)	–	–	–	++ (5 cm. *long)*	10 cm. long	Not mentioned	Right	Orchidectomy
(4)	++ (shaving 2 *years)*	–	–	+	Not mentioned	Not mentioned	Right	Orchidectomy
(5)	–	+	–	+ (feminine distri.)	Genitals enlarged	Not mentioned	Left	Orchidectomy
(6)	–	+	+	+	Enlarged	Not mentioned	Left	Orchidectomy
(7)	+	–	+	+	Enlarged	Not mentioned	Right	Orchidectomy
(8)	–	+	+	++	Pronounced enlargement	Not mentioned	Left	Orchidectomy
(9)	–	–	+	+	Genitals	Frequent	Right	Orchidectomy
(10)	–	–	–	+	8 cm. long, 9 cm. circumference	Present	Right	Orchidectomy

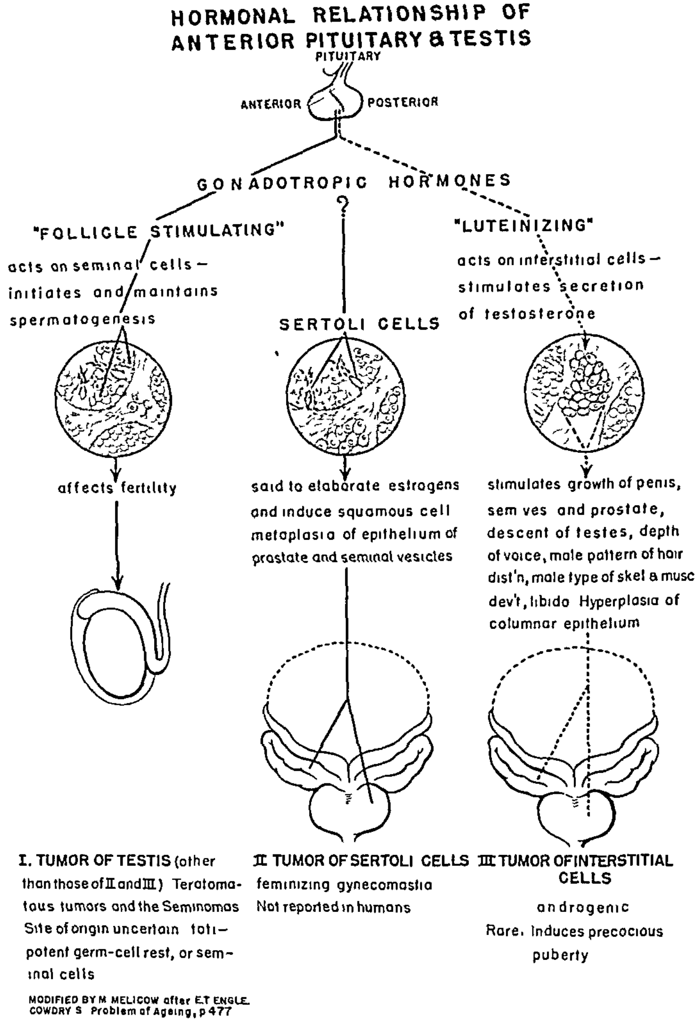
TABLE 2—*Continued*

UTHOR	DESCRIPTION OF TUMOR	FOLLOW-UP
(1)	Weight 289 grams	Regression of beard and voice. Mustache persisted. No change after 10 months
(2)	Left testis 5× size of right. Brownish tumor	No regression 2 years post-operation
(3)	Weight 210 grams. Spermatogenesis in neighboring tubules	X-Ray· sella neg. IVP neg. No adrenal enlargement. Friedman Test neg. No calcium in pineal region. Regression of hirsutism but at 14 mo. post-operation no voice change
(4)	Size of orange. Pinkish brown. Hemorrhages	No regression 18 months post-operation
(5)		Genitals smaller. No regression of pubic hair or breast
(6)	Weight 130 grams. Dark brown	Metastasis to liver produced male hormone
(7)	Not mentioned	Slight regression 3.5 months postoperation. No voice change
(8)	Not mentioned	Will be reported at later date by Dr. Ph. R. Rezek
(9)	Yellow-gray oval mass	Main symptoms regressed after operation
(10)	Brownish discrete mass	No regression after 6 months

believes that the interstitial cells are normally infiltrating in nature, and may therefore be present in the lumen or walls of tubules and yet not be malignant. Berger found interstitial cells in the tunica, in the hilar region, and around nerves, and proposed the term "sympathicotropic" or "hilus" cells. Nelson also found them in these areas but favors the name "extraparenchymal" interstitial or Leydig cells.

The number of interstitial cells varies in different individuals and in the different periods of development of any one individual (Sands and Okkels), and at times are hard to find. There is a seasonal variation in some species.

Interstitial cells are numerous in fetal life, probably because of the increased activity of the maternal anterior pituitary-like hormones. At birth, a pronounced reduction occurs, but at puberty they again increase, and continue to do so until they attain their maximum number at maturity. In more than 500 testes examined by Teems, it was found that the interstitial cells were most numerous between the ages of 10 and 19. Thence they gradually diminished, but their size, granule and pigment content increased up to the age of 40.


HORMONAL RELATIONSHIP OF ANTERIOR PITUITARY & TESTIS
PITUITARY
ANTERIOR
POSTERIOR
GONADOTROPIC HORMONES
"FOLLICLE STIMULATING"
acts on seminal cells – initiates and maintains spermatogenesis
?
"LUTEINIZING"
acts on interstitial cells – stimulates secretion of testosterone
SERTOLI CELLS
affects fertility
said to elaborate estrogens and induce squamous cell metaplasia of epithelium of prostate and seminal vesicles
stimulates growth of penis, sem ves and prostate, descent of testes, depth of voice, male pattern of hair dist'n, male type of skel & musc dev't, libido Hyperplasia of columnar epithelium
I. TUMOR OF TESTIS (other than those of II and III) Teratomatous tumors and the Seminomas Site of origin uncertain toti-potent germ-cell rest, or seminal cells
II TUMOR OF SERTOLI CELLS feminizing gynecomastia Not reported in humans
III TUMOR OF INTERSTITIAL CELLS androgenic Rare. Induces precocious puberty

MODIFIED BY M MELICOW after E.T ENGLE
COWDRY S Problem of Ageing, p 477

FIG. 4

TESTOSTERONE

The interstitial cells from boyhood to late middle life constitute an active endocrine organ producing the male sex hormone. The latter is absorbed by the general circulation, exerts its effect upon various organs and tissues, and is broken down to androsterone and other excretory products. David, Dingemanse, Freud and Laqueur isolated testosterone, the true primary androgen. Synthetic production of the hormone using cholesterol as starting material was first accomplished by Butenandt and Hanisch.

Testosterone stimulates the growth and development of the penis, seminal vesicles and prostate, and participates in producing the descent of the testes, the depth of voice, distribution of facial and body hair in male pattern, male type skeletal muscular development, and libido. The testis cannot be stimulated by the male hormone directly but via the pituitary (fig. 4).

Androgens are reduced in castrate males, eunuchoids, and in some patients with gynecomastia. They are decreased in cryptorchidism, yet most adults with undescended testes show an increase in the number of interstitial cells. Androgens are said to be reduced in patients with so-called benign hypertrophy of the prostate. One would expect the opposite in view of the trophic effect that these cells have on the prostatic urothelium. There is no evidence of interstitial cell hyperplasia in testes of patients with carcinoma of the prostate, yet the beneficial effects of bilateral orchidectomy seems to be due to the removal of the influence by the Leydig cells. Spermatogenesis may be inhibited temporarily by the administration of male hormone.

REVIEW OF LITERATURE

Reports on interstitial cell hyperplasia and neoplasia fall into four categories:

1) Cases with interstitial cell hyperplasia. They were usually accidental findings and occurred in all age groups. Endocrine disturbances were rare.

2) Cases of interstitial cell tumor.

a) Some developed in children, were associated with precocious puberty and were usually benign (table 2).

b) Some developed in adults, were without obvious endocrine disturbance in the majority, but with loss of libido and development of gynecomastia in some (about 15%) (table 3).

3) Reports of interstitial cell tumors in animals (mostly dogs and horses).

4) Experimental production of interstitial cell tumors in lower forms, mainly in mice, by means of estradiol benzoate or triphenylethylene or stilbestrol.

1. *Interstitial cell hyperplasia.* Hyperplasia is more common than tumor. Warren and Olshausen noted that artificially imposed conditions which cause a decrease in spermatogenesis seem to stimulate the proliferation of interstitial cells. Hyperplasia has been found following vasectomy, partial castration (Kraus), testicular grafting, change in environmental temperature (warmth), X-ray (Kyrle) and radium radiation, dietary deficiency (vitamin E), injection of some drugs and administration of some glandular extracts. Spangaro noted an increase in interstitial cells under the following conditions: in some atrophic senile testes, the degree of hyperplasia being directly proportional to the stage of atrophy; in some normal senile testes; in association with chronic illness; tuberculosis, cancer, syphilis, pernicious anemia, cirrhosis of the liver, diabetes; in

atrophy of testes associated with hypothyroidism (Marine); in chronic alcoholism; in acute illness (pneumonia); in undescended and ectopic testis; in pseudohermaphroditism; following compression of the cord, stricture or ligation of the deferens, funiculitis and chronic disease of the prostate and bladder. It was our impression that interstitial cell hyperplasia tended to occur in testes that were smaller than normal, that the process was intertubular, not demarcated, and that it was probably more common than is indicated by the reports (fig. 3).

Table 1 presents in chronological order the cases of interstitial cell hyperplasia which we reviewed.

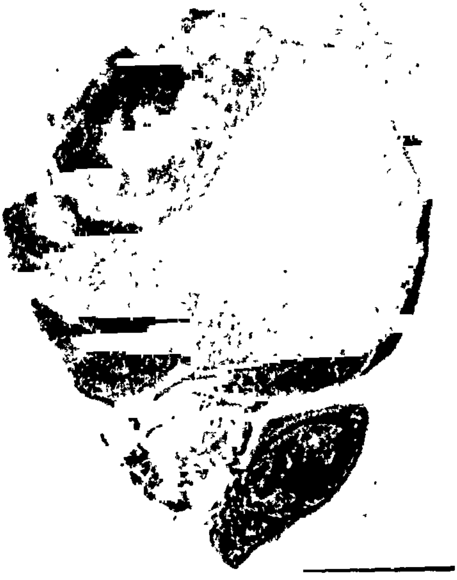


FIG. 5. Stewart, Bell and Roehlke's case. Cross section of tumor.

2. *Tumors of the interstitial cell.* a) In children: The majority were discovered following the development of precocious puberty between the ages of 4½ and 5 years. All presented macrogenitosomia, pubic hair, and adult male voice. The tumors were benign in all except 1 case, and removal resulted in regression in one-third of the cases, slight regression in another third, and no change in the remaining third. The facial beard persisted, the pubic hair development was retarded in some, and axillary hair was absent or delayed in the majority. In a number of cases erections were mentioned as being present before operation, in a few ejaculations were also noted, as was spermatogenesis. In interstitial cell hyperplasia groups of cells were sporadically spread between tubules; in tumors, however, the mass of cells was found to be concentrated and demarcated from

neighboring tubules. In some cases, it looked as if the tumor could have been shelled out of the testis without removing the latter. The cells retained their characteristic appearance but simulated liver cords. At times they resembled the fascicular "foam" cells of the adrenal gland but the characteristic elliptical shape of the interstitial cells and their eccentric pale nuclei with prominent eosinophilic nucleoli aided in differential diagnosis.

b) In adults: Tumors of interstitial cells of the testis in adults were usually unassociated with any obvious endocrine disturbance. They were difficult to recognize until they attained a size sufficient to produce local symptoms. The majority were benign, a few were malignant. Some may have been accompanied by an increased excretion of the degradation products of male hormones but only in a few instances were such assays made. Some of the cases may have been variations of other types of testicular tumors, erroneously interpreted as interstitial cell tumors. A number were associated with a paradoxical endocrinological dyscrasia: instead of increased masculinity, there was atrophy of genitalia, loss of libido, aspermia, and gynecomastia. It was difficult to explain this reversal in an adult male with a tumor that manufactured testosterone. Perhaps the hyperplasia of the interstitial cells was a response to a hidden powerful estrogenic agent. The experiments of Bonser in which interstitial cell tumors were obtained in male mice by the injection of estradiol benzoate and triphenylethylene suggest such a possibility.

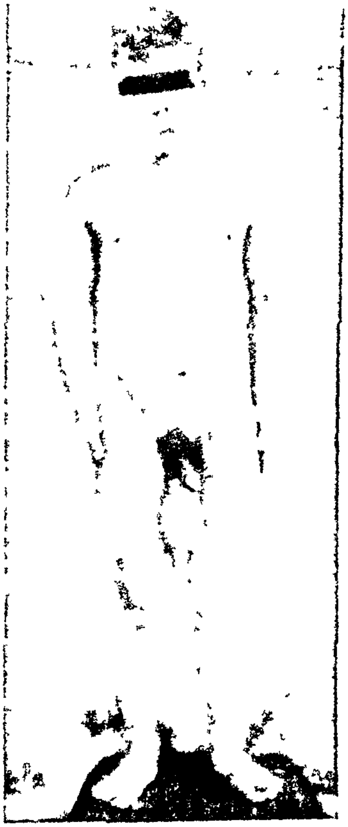


FIG. 6. Somerford's case. Patient aged 11. Note pubic hair and enlarged scrotum.

Gynecomastia Gynecomastia was found in 15 per cent of adult males who had either interstitial cell hyperplasia or tumor (Edmondson) Huffman's case (table 2) was the only instance of gynecomastia in a child (age 6)

It should be noted that gynecomastia has been observed under a variety of conditions and is not pathognomonic of any single endocrine organ disturbance Gilbert differentiates between choriogenic and physiologic gynecomastia The former is due to stimulation by chorionic epithelium, such as is observed in trophoblastomas (chorio epitheliomas) of the testis The breasts enlarge, they may secrete, and the areolae increase in size and become deeply pigmented The estrin and gonadotropin assay of the urine is usually high In physiologic gynecomastia, the breasts do not secrete, the areolae are not enlarged or pigmented, and the gonadotropic titer of the urine is either normal or slightly increased

Gynecomastia has been seen in the following conditions

During puberty Nearly all boys have unilateral or bilateral breast enlargement at puberty, but it is usually slight, often unnoticed and recedes rapidly (Weber) It may increase on one side and regress on the other (Jung and Shafton)

Following destruction (traumatic) or atrophy of testes in young adults (Apert and Decléty)

Occasionally in association with·

1) Disturbances in the pituitary gland
2) Tumors of the pineal gland
3) Hyperthyroidism
4) Cirrhosis of the liver Glass et al found atrophied testes in cases with hepatic cirrhosis and also an increased partition of free estrin as opposed to conjugated estrin Failure of the liver to properly metabolize estrin results in hyper estrinism and ensuing gynecomastia (Tattoni, Bailey)
5) Adrenal cortical tumors Hyperfunction or hyperplasia or tumor of the adrenal cortex is usually associated with an increase in androgens Such a condition induces virilism or the adrenogenital syndrome in women The cortex can also produce estrogens and increase of the latter may cause "feminization" in the male atrophy of testes, aspermia, loss of libido, and gynecomastia
6) Post prostatectomy Rare and usually in elderly patients (Kondoléon, Petit de la Villéon, Oppenheimer)
7) Tumors of the testes The association of gynecomastia with testicular neoplasms has been noted on frequent occasions Rubens painted a Kaffir with large breasts and unilateral enlargement of the scrotum Gilbert found 135 cases of gynecomastia in 7000 testicular tumors They were divided into 3 groups a) those that were associated with choriogenic tumors (trophoblastomas), b) those that were associated with non choriogenic tumors, such as teratomas (Cairns), carcinomas, seminomas, etc , and in whom the enlargement may have followed atrophy of the remaining testis following radiotherapy Here, the gynecomastia may have resulted from the unopposed activity of the Sertoli cells which are said to secrete estrogens (Huggins), c) those that were associated with tumors of the interstitial cells They occurred chiefly in adults This puzzling syndrome, viz , increase in interstitial cells and development of gynecomastia

AUTHOR	YEAR	AGE	SIDE	GYNECO-MASTIA	POTENCY	DESCRIPTION OF TUMOR	DIAGNOSIS	REMARKS
Waldeyer	1872						Plexiform angiosarcoma	
Hansemann	1895						Alveolar sarcoma	Probably seminoma
Pick	1905							
Chevassu	1906	27	Left, ectopicing.			Hen's egg Reddish-yellow	Interstitial cell tumor	Alive 22 months post-operation
Kaufmann	1907	30	Bilat.			210 gms.; 140 gms. Rusty brown	Interstitial cell tumor	Resemble liver cords or adrenal cortex or alveolar tumor
Kaufmann	1908	34	Unilat.			140 gms.	Interstitial cell tumor	Brother of preceding case. No Reinke's crystals.
Stoppato	1911	32 26 ?						All probably seminomas
Masson and Sencert	1923	62	Unilat.		Diminished libido	Painless	Interstitial cell carcinoma	Married. 3 years, 10 months after operation: metastases to groin, femur, lung; iliac, lumbar and mesenteric lymph glands. Died 4 years, 4 months after appearance of tumor. Cells resemble liver cords or adrenal
De Josselin de Jong	1926	42	Unilat.			Intra-abdominal. Size of child's head	Interstitial cell carcinoma (?)	Opposite testis atrophic with interstitial cell hyperplasia. Metastases. Died
Menaschkin	1926	30	Right. Atrophy left	Bilateral			Interstitial cell tumor	Right orchidectomy and right mastectomy. Regression of left breast and enlargement of left testis to normal size
Villata	1925	22	Unilat. Inguinal canal				Interstitial cell tumor	Probably teratoid (Jemerin)
Slanina	1930	45	Unilat.			94 gm	Interstitial cell tumor	Probably teratoid (Jemerin)
Pitrolffy-Szabó	1930	40	Left		Potent		Interstitial cell tumor	External genitalia of feminine appearance; hypospadias. Characteristic of pseudohermaphrodite. Married. One child. Normal sex life

Pana	*1931*	*16*	*Unilat. Scrotal*			28 gms.		*Opposite was inguinal, 3 5 gm.*
Rigoletti	1936	35	Bilat.					
Budd	1937	42	Right	Present	Impotent	Encapsulated. Yellowish-white. 2 x 2 x 2 5 cm	Interstitial cell tumor	Assay of urine negative for prolan. 20 mu of Estrin in 1 73 gm tumor. 3 mo p o: breasts smaller; impotentia partially overcome. 28 mo. p. o.: no metastasis. Libido returned. (E. T. Bell thought it was embryoma)
Jemerin	1937	35	Left		Potent, live spermatozoa	Dark brown	Interstitial cell tumor	Resemble liver cords. No Reinke's crystals
Braun	*1939*	*45*	*Unilat Autopsy*				Interstitial cell tumor	Patient died, carcinoma of stomach. Findings in testis at autopsy.
Fialho	1941	44	Unilat				Interstitial cell tumor	
Warren and Olshausen	1942	30	Unilat			Brown	Interstitial cell tumor	
Masson and Venning	1942	32	Unilat				Interstitial cell tumor	Urine 17-ketosteroids above normal (950, 1035, 1040 mg /24 hrs). Metastases 10 years after appearance of tumor and 9 years postoperation
Bonser and Hawksley	1943	40	Left		Potent		Interstitial cell tumor	Well 3 years postoperation
Bonser and Hawksley	1943	31	Left		Impotent	Brown. Limiting capsule. Painless	Interstitial cell tumor	Well 6 months postoperation
Neeve and Marsh	1944	48	Right		Potent	Pinkish brown	Interstitial cell tumor	
Edmondson	1944	30	Unilat	Bilateral			Interstitial cell tumor	No regression 3 years postoperation
Edmondson	1944	32	Unilat				Interstitial cell tumor	No endocrine disturbance
Edmondson	1944	82	Unilat.				Interstitial cell tumor	Malignant *No endocrine disturbance*

may be the result of an overwhelming estrogenic influence, the former representing a compensatory mechanism and the latter a functional response.

8) *Following the injection of testosterone:* McCullagh and Rossmiller in 1941 reported gynecomastia developing in hypogonad males who received injections of methyl testosterone over a prolonged period. Oligospermia was also observed.

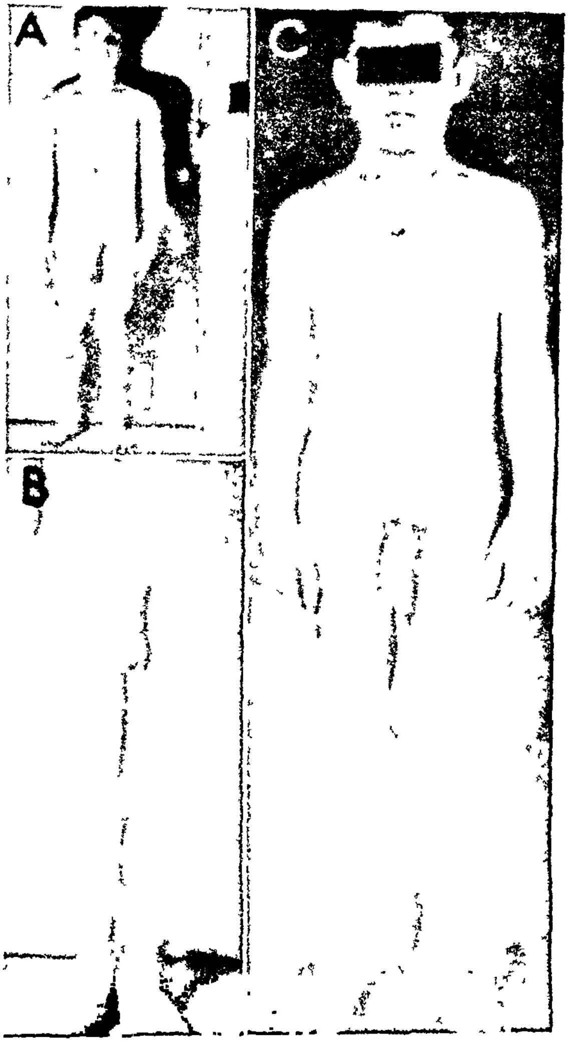


FIG. 7. *A* and *B*, Rezek's case. Patient aged 10. Note muscularity, hirsutism and enlarged penis. *C*, Werner's case. Patient aged 6. Note macrogenitosomia.

Selye et al. in 1936 obtained milk secretion in male rats, both normal and castrate, by the administration of testosterone.

9) ? Unopposed activity of Sertoli cells: Huggins reported Sertoli cell tumors of the testis in 5 dogs. They were associated with mammary enlargement and had other evidence of feminization. He is of the opinion that the Sertoli cells can manufacture estrogen whose excess may induce gynecomastia. No similar tumors have been reported in man.

3. *Interstitial cell tumors in animals.* Interstitial cell tumors of the testis have been found in dogs, horses, mules, rabbits and in hybrid birds. Interstitial cell

hyperplasia was often present in the cryptorchid testes of horses, dogs, rabbits, and in the testes of old dogs Innes noted that by 1942, 260 tumors of this type were found in dogs Endocrine disturbances such as occurs in humans, especially in children, were not described

TABLE 4 *Interstitial cell tumors in animals*

AUTHOR	YEAR	ANIMALS	REMARKS
Ball	1913	Dogs	
Kuntze	*1916*	*Dogs*	*15 interstitial cell out of 23 testicular* tumors, usually in atrophic testes in those of old dogs Were multiple, often bilateral ? Hyperplasia (Jemerin)
Poll	1920	Male peacock and guinea hens	2 cases
Ball	1922	Dogs	2 interstitial cell tumors
Pallaske	1931	Dogs	31 interstitial cell tumors out of 38 (in 107 dogs)
Blanchard *et al*	1936	Dogs Horses	4 interstitial cell tumors in 85 old dogs 2 interstitial cell tumors
Peyron, Blanchard and Salomon	1936	Dogs	31 interstitial cell tumors in old dogs
Schlotthauer	1938	Dogs	51 interstitial cell tumors in 82 dogs, average age 12 years Brown tumors In 5 cases, seminoma and interstitial cell tumors were associated 9 were multiple
Salomon	1938	Dogs	*41 interstitial cell tumors out of 71 tumors* (in 393 dogs)
Innes	1942	Dogs Calf	2 interstitial cell tumors, 12 hyperplasia *of interstitial cells* 1 interstitial cell tumor

Table 4 summarizes some of the reports

4 *Experimental production of interstitial cell tumor of testis* Interstitial cell tumors of the testis have been produced experimentally following the injection of female sex hormones into immature male mice Bonser and Robson injected estradiol dipropionate and triphenylethylene into mice of strains R III and CBC, and triphenylethylene only into Strong A strain In the latter strain, they

noted interstitial cell hyperplasia and later benign tumors and, finally, histologically malignant tumors. Hooker et al. in 1938 gave a mouse weekly injections of 0/05 mg. estradiol benzoate in sesame oil beginning at 30 days of age. After 6 months, the left testis was the seat of an interstitial cell tumor which later metastasized. In 1942, Bonser reported another series of benign and malignant interstitial cell tumors in estrogen-treated Strong A mice. She gave weekly injections of 3 mg. triphenylethylene in sesame oil to ten 4-weeks old Strong A male mice, and all of the 8 that survived 50 weeks had bilateral interstitial cell tumors. In 2, the tumors were malignant. Shimkin et al. implanted 4–6 mg. stilbestrol pellets into 3 weeks to 3 months old 107 C. male mice, and 3 to 5 months later noted atrophy of the seminiferous tubules, aspermatogenesis, and diffuse hyperplasia of the interstitial cells. In 11 months, 13 tumors, 2 of which were bilateral, developed. Bouin and Ancel found interstitial cell hyperplasia in rabbits after tying off the vas deferens. Warren and Olshausen noted that the prolonged injection of prolan A in infant and adult mice and rats results in an increase in the interstitial cell elements. Except for the latter finding, it is apparent that in animals those factors which decrease testicular tubules and spermatogenesis, stimulate an increase in interstitial cells.

SUMMARY

A case of an interstitial cell tumor of testis in a 5½ year old boy has been presented and added to the 9 cases previously reported. A review of interstitial cell hyperplasia and of neoplasia in adults and in animals has been included. The subject of gynecomastia and the experimental production of interstitial cell tumors were discussed.

CONCLUSIONS

Tumors of interstitial cells of the testis are rare. Ten cases in children and 27 in adults have been reported to date.

In children, they tend to induce precocious puberty with macrogenitosomia. The tumors are usually benign but removal is rarely followed by adequate regression. However, in none of the cases was the postoperative follow-up longer than 2 to 3 years.

In adults, interstitial cell tumors are usually not associated with any obvious endocrine disturbance. About 15 per cent presented gynecomastia, loss of libido and atrophy of gonads. The majority improved after operation.

An interstitial cell tumor develops as a brownish, discrete, localized mass within the testis. Interstitial cell hyperplasia is characterized by a diffuse increase in the number of interstitial cells between tubules.

Interstitial cell hyperplasia is probably considerably more common than statistics indicate. It is usually present when seminiferous tubules suffer injury or atrophy or when spermatogenesis is retarded or destroyed.

Interstitial cell hyperplasia and tumors are not uncommon in dogs, horses, etc. They are prone to occur in cryptorchids and in testes of old animals.

Though prostatic epithelium is under the influence of testosterone, the expected increase in interstitial cells in cases with "prostatic hypertrophy" and carcinoma is not borne out by microscopic studies.

The injection of female sex hormone in immature male mice is frequently followed by the development of interstitial cell tumors.

Gynecomastia occurs under a variety of conditions and is not pathognomonic of any one particular endocrine dyscrasia. The association of gynecomastia, gonadal atrophy and loss of libido with tumors that manufacture testosterone is puzzling. It is of interest to note that McCullagh and Rossmiller reported gynecomastia in males who had received large doses of testosterone. The condition regressed when the hormone was discontinued.

The authors express their thanks to Dr. A. P. Stout for valuable suggestions and to Dr. Ph. Rezek for the inclusion of his case.

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ATYPICAL CYTOLOGY IN TESTES BIOPSIES[1]

EARL T. ENGLE

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Abnormal spermatozoa are found in varying proportions in the semen sample. In men with low sperm counts there is usually a high percentage of abnormal forms (McLoed, 1946; Simmons, 1946).

The relation of atypical cytology in the testis to the presence of abnormal forms in semen appears to be of some interest. A statistical study of cell types will be presented later. The present report includes some correlations of significance in a few recent representative cases, chosen from a considerable series.

These cases represent a group of men with oligospermia, having a large number of abnormal sperm on repeated examination, and on whom testes biopsies have been done. Examination of these tissues has shown that in many cases with a high incidence of abnormal forms, characteristic defects of nuclear structure and cell division are very numerous in the testis. The nature or cause of these defects is not not known.

CASE REPORTS

Case 1. L. F. (P. H. No. 930893), a 37 year old white salesman, under the care of Dr. John Lattimer, was admitted to Presbyterian Hospital with a complaint of a right hydrocele and sterility. This man had been married for 7 years and had used no contraception. Two episodes of rheumatic fever had resulted in hospitalization for 3 months in 1941 and again in 1944. He had attended the Sanger Clinic for 1 year, without treatment. His sperm count was about 1 million per cubic centimeter with no normal forms.

Bilateral testis biopsy was done at the time of reduction of the hydrocele.

Right testis: Tubules very unequal in size. Basement membrane and tunica propria not thickened. Spermatogonia and primary spermatocytes normal in number. There are a great number of primary spermatocytes in mitotic division. (Mitotic spindles are quite rare in normal testis.) Secondary spermatocytes are not numerous. The nuclei are pyknotic and fragmented. Spermatids are atypical, amorphous pyknotic granules. Many multinucleate cells. Normal spermatozoa are rare. Intertubular tissue normal. Arterioles normal.

Left testis: Condition the same.

Impression: Incomplete maturation of spermatozoa due to chromosomal aberration or other physical factors affecting final stages of sperm formation. The factors involved are uniform as all tubules in both testes present the same condition.

The points of interest in these testes are that the spermatogonia and primary spermatocytes are normal in number and in structure. The number of primary spermatocytes in mitotic division is excessive, while the cells normally resulting from this cell division are few and are not normal.

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[1] Acknowledgement is made of the generous cooperation of Dr. George F. Cahill, director of Squier Urological Clinic of the Presbyterian Hospital and to others of the staff, particularly Dr. George Barrett, chief resident urologist.

The sex chromosomes, x and y, are clearly visible on many of the spindles (figs. 1, A and B, and 2). Under normal conditions, the primary spermatocyte, containing 46 chromosomes, divides into two secondary spermatocytes. Each of these later cells contains the reduced number of chromosomes, 23 plus either an x or a y chromosome.

The essential defect appears to lie in the inability of the primary spermatocyte to pass through this reduction division phase. A limited number of spermatozoa are produced but there are no normal forms. There are no suggestions of a constitutional disorder, unless the episodes of rheumatic fever be so considered.

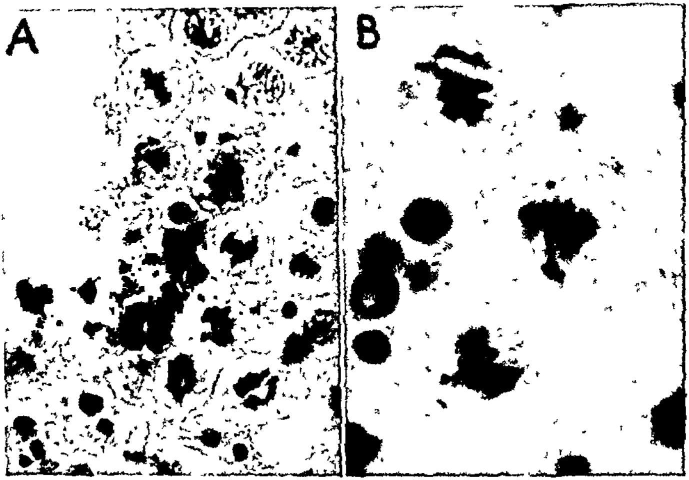

FIG. 1. Case 1 A, microphotograph of testis biopsy, showing seven mitotic figures of primary spermatocytes in one microscopic field. The nuclear debris are the result of failure of successful cell divisions. B, microphotograph of 3 cells shown in A. In the cell in the center of the field the elongated chromosome designated x is seen at one pole of the spindle and the round y chromosome is seen near the other pole.

Hormone assays show gonadotrophins of 20 mouse uterine units per 24 hours (Levin's method) which is quite normal.

This type of case belongs in the category previously designated as *spermatogenic arrest* (Engle, 1946).

Case 2. J. H. (P. H. No. 926659), a 25 year old office worker, a patient of Dr. John Robinson, had been married 4 years with no conceptions. Appendectomy at age 15. Patient had always had good health. Patient's previous history contributed nothing to the present fertility problem.

Except for semen analysis all other examinations were normal. Ten sperm

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The points of interest in these testes are that the spermatogonia and primary percentage of abnormal forms, in these specimens over the 2 year period. A bilateral testis biopsy was done.

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Right testis: Tubules normal in size and configuration. There is a slight but uniform hyalinization of basement membrane. Cell population appears normal. Atypical spermatogonia are numerous. These cells are very large and contain 2 or more atypical nuclei of unequal size. Great numbers of mature spermatozoa attached to Sertoli cells. Very few normal sperm heads—macronuclei and beaded forms abundant. Interstitial cells normal with crystalloids. Arteries appear normal.

Left testis: Tubules normal size and configuration. Very slight hyalinization on some tubules. Cell population normal. Spermatids and spermatozoa numerous. Abnormal forms very numerous, particularly macro forms. Intertubular tissue and arterioles apparently normal.

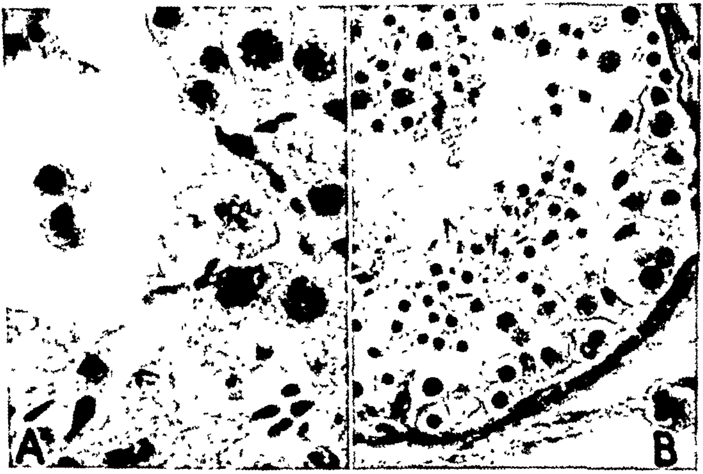

FIG. 4. Case 2. *A*, microphotograph of testis biopsy, showing abnormal sperm heads, with giant forms, dumb-bell and beaded forms. *B*, microphotograph of testis biopsy, same as shown in *A*. Atypical multinucleate spermatogonia are shown.

Diagnosis: Normal testes with abnormal spermatozoa (fig. 3).

The structural defect in this case appears to be faulty cell division in the spermatogonia, with resulting disturbances in later cell generations, resulting in sperm with giant or beaded heads (fig. 4), contrasted with normal sperm (fig. 3).

The spermatogonia are the primitive embryonic germ cells which migrate into the testis early in embryonic development. They are the only cells of the germ cell line present in the testis at birth. The next stage, the primary spermatocyte, appears before puberty. It is not known if this defect is a constitutional one or if some real deficiency exists. If such deficiency is to be suspected it is probably not due to one of the hormones now known.

Case 3. A. M. (P. H. No. 920099), was a 29 year old Italian sewing machine operator who came to New York at the age of 10. His basal metabolism rate was −12, Kline negative, complete blood count negative. X-ray was negative except for a spina bifida of L.5. The left testis was cryptorchid. Pre-biopsy sperm counts of 8 and 10 million per cubic centimeter showed few sperm with normal morphology.

Biopsy of the scrotal right testis was done.

Right testis: Specimen consists of a large, carefully excised piece of testis tissue. Tubules are uniform in size and configuration. There is a slight thickening of the basement membrane, which may be without significance. Cell population within the tubule greatly reduced. A few tubules with no germinal epithelium, consisting only of Sertoli cells.

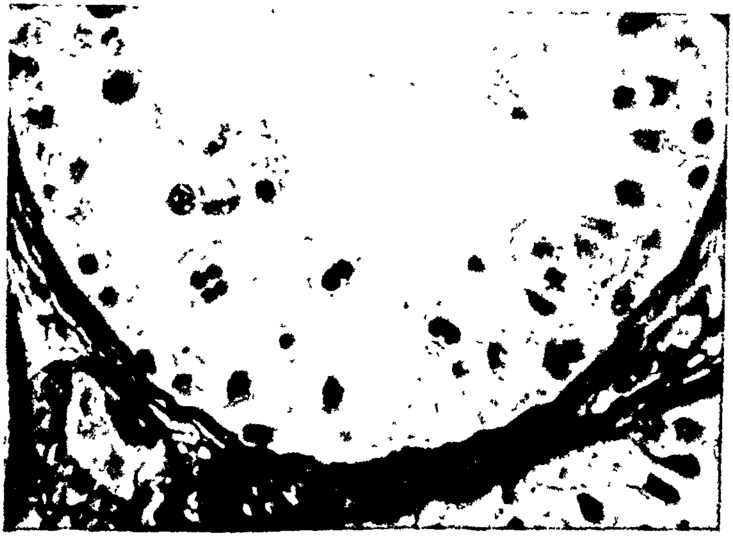

FIG. 5. Case 3. Microphotograph of testis biopsy. Nuclear abnormalities of spermatogonia and primary and secondary spermatocytes are shown.

Spermatogonia line the basement membrane of most tubules. Many of these are exceptionally large cells with much cytoplasm. One or more spermatogonium in each tubule is a bi- or multinucleate form. In at least one instance the nucleus can be seen dividing amitotically. Primary spermatocytes vary greatly in numbers among different tubules. Many spermatocytes 1° are exceptionally large cells with large nuclei, in which the chromatin is arranged in a loose spireme. Some disintegrated cells lie free in the lumen, containing great masses of chromatin.

Secondary spermatocytes not numerous. Some appearing normal, others pyknotic and many multinucleate forms. Sperm heads are infrequent, and rarely in the Sertoli cells. Many giant sperm heads, many with club-like heads. The Sertoli cells have fuchsinophile crystalloids.

Intertubular tissue normal. Interstitial cells numerous, with crystalloids. Arterioles normal.

Diagnosis: Reduced spermatogenesis through aberrant cell divisions.

As in the previous case, the defects in cell division can be found in the spermatogonia, and seen in each subsequent stage of sperm development (fig. 5).

Case 4. R. F., a 27 year old business man, a patient of Dr. John Robinson, had some degree of cryptorchidism at 12 years of age. Complete descent occurred after 2 years of treatment elsewhere, probably with chorionic gonadotrophin.

Other history was noncontributory. Basal metabolism rate, complete blood count and other laboratory tests were normal. Patient had been married 7 years with no conceptions.

Examination of semen specimens had been made on four occasions preceding testis biopsy. The volume was from 4.5 to 5.5 cc with counts ranging from 10 million to 27 million per cubic centimeter. The percentage of normal forms of spermatozoa ranged from 0 to 50 per cent.

Right testis: Tubules uniform in contour, equal in size. Basement membrane and tunica propria not thickened. Cell population normal in number. All stages of spermatogenesis present in proper proportions. No unusual nuclear abnormalities noted in cell lineage below spermatids. The spermatids and maturing spermatozoa show a great diversity of form. Some have macronuclei; many show dumb-bell, or club-shaped forms.

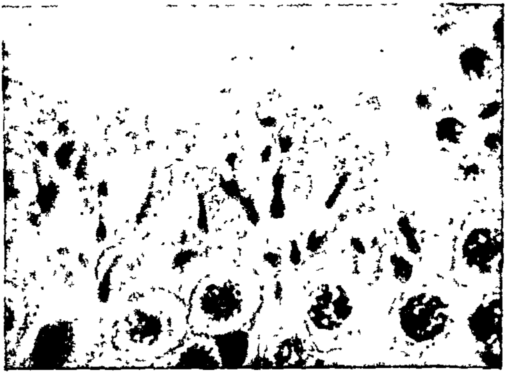

FIG. 6. Case 4. Microphotograph of testis biopsy, showing the abundance of abnormal sperm heads.

The arterioles of the intertubular areas show marked sclerosis. The muscular media is mostly replaced by hyalinized collagenous tissue. There are sclerotic plaques in the intima.

The left testis is quite similar.

Subsequent examination did not reveal any evidence of systemic arteriosclerosis. The arteriolar lesions in this pair of testes were pronounced.

The histological status of these testes is quite different from those described above. Nuclear abnormalities could not be detected in stages prior to the spermatid (fig. 6), that is the spermatogonia, and primary and secondary spermatocytes showed no structural aberrancies. The end result, abnormal sperm heads, however, was the same as in cases 2 and 3. Disturbances in oxygen distribution and other metabolic effects of arteriolar damage cannot be ignored as possibilities in these cases.

SUMMARY

Atypical cytology and aberrant mitotic cell divisions were observed in testis biopsies of men with consistently low sperm counts and with high percentages of abnormal spermatozoa.

The degree to which these frequently occurring cytological phenomena in the testis may represent deficiencies in substances necessary for normal cell division is, of course, unknown. These cases do not appear to be the result of inadequacies of any known hormones.

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TORSION OF THE SPERMATIC CORD[1]

SAM PECK

This discussion is based on 6 patients seen by the author. The first 4 were seen at the Letterman General Hospital, where the clinical data were assembled by permission of Dr Oscar F Nolan (deceased), who was chief of the Urology Section The fifth patient was seen at the 191st General Hospital in Paris, France, and recorded by permission of Dr William H Field, who was Chief of Surgery there The sixth was seen in private practice

Torsion of the spermatic cord must be considered in the investigation of any acute pathological condition of the scrotum or groin, but may even occur with an intra-abdominal testis, producing severe lower abdominal pain The most common conditions from which it must be differentiated are: 1) acute epididymitis, in which there may be a history of urethritis, the finding of objective evidence of infection in the genito urinary tract, and a thickened, palpable epididymis located posterior to the testicle, 2) strangulated inguinal hernia, 3) acute hydrocele, usually less painful and easily transilluminated 4) acute orchitis, 5) tumor of the testicle, which occasionally has an acute onset, 6) suppurative inguinal adenitis, 7) torsion of the appendix testis (hydatid of Morgagni), a remnant of the cephalic end of the mullerian duct, normally attached by a pedicle to the upper end of the testis and capable of torsion and a clinical picture easily confused with the subject being discussed, though less severe

Clinical types of torsion of the spermatic cord are the acute and the chronic recurring varieties The anatomical types are 1) the more common intravaginal type in which the twisting of the testicle and epididymis occurs within the tunica vaginalis (fig 1, *B*), and 2) the more rare extravaginal form, in which there is a twisting of the entire spermatic cord above the tunica vaginalis (fig 1, *A*) This is more frequently seen in the undescended or intra abdominal testicle

The predisposing causes of torsion are 1) hypermobility of the testicle, often associated with a history of late descent into the scrotum, 2) tumors of the testicle, 3) a large and roomy tunica vaginalis testis, 4) faulty development or absence of the mesorchium, 5) high investment of the tunica vaginalis on the cord, 6) absence or faulty development of the gubernaculum testis, 7) abnormal attachment of the spermatic cord to the testicle, so that a large portion of either or both poles of the testicle lies free within the tunica vaginalis, 8) excessive length of the spermatic cord, 9) inversion of the testicle, 10) cryptorchidism

The most common exciting factor for torsion, given any or all of the above predisposing factors, is any movement which induces a strong contraction of the cremasteric muscle The end result, if the torsion is unrelieved, is an aseptic gangrene of the testicle and contiguous structures

Symptoms are characterized by a sudden onset of acute pain, usually preceded by some form of exercise, but occasionally seen in patients lying quietly in bed. The pain may be accompanied by nausea, vomiting, and mild shock. Very rarely has torsion been described as occurring without pain of any importance.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif , January 17, 1949

The findings on physical examination are characteristic:

1) Swelling of the testicle and epididymis. Often there is redness and some edema of the scrotal skin or in the inguinal region in undescended testicle. The scrotal skin may be contracted.

2) If swelling and edema are not too marked it may be possible to palpate the epididymis in an abnormal anterior position.

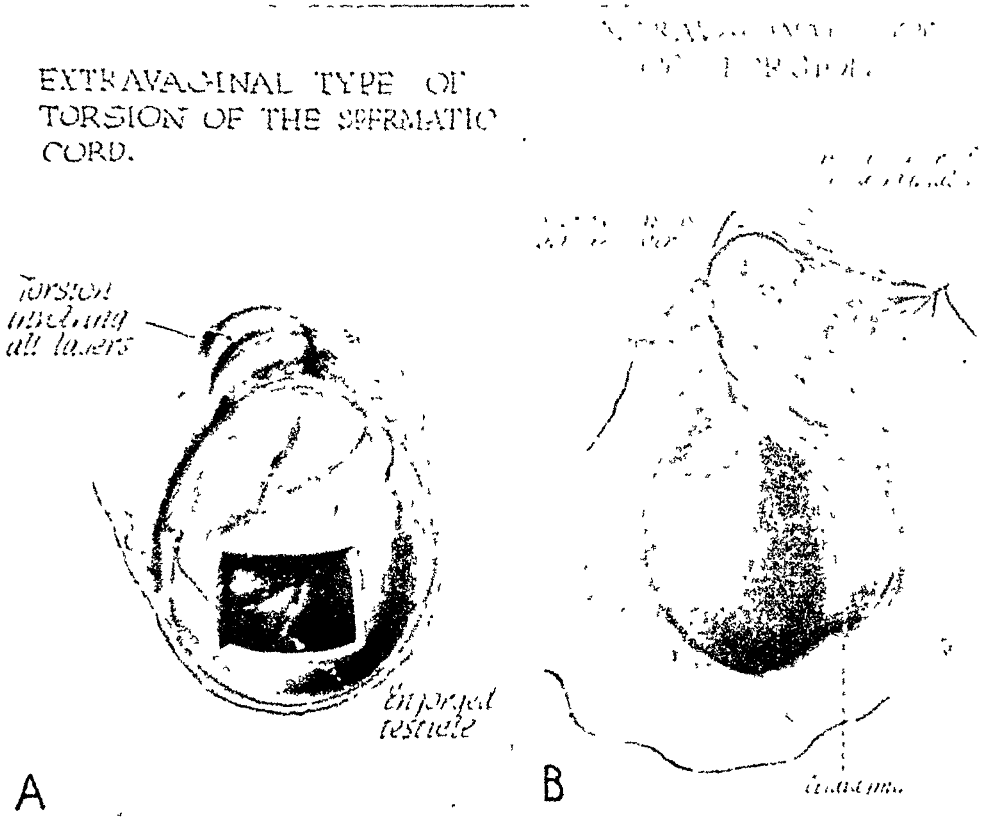

FIG. 1

3) Prehn's sign. Theoretically, elevation of the scrotum is analgesic in inflammations within the scrotum, and conversely aggravates the pain in torsion of the spermatic cord. In the cases we have seen movement of the scrotum in any direction aggravated the pain.

4) There is no impulse on coughing.

5) The thigh on the affected side is often held in flexion.

REPORT OF SIX CASES

We can add little if anything to previous careful discussions of this problem, especially the excellent paper by Ormond in the J. A. M. A. He stressed certain criteria for the prompt diagnosis of the condition, which our cases met in most instances, but not at all in others. The following important findings have been stressed by all writers on the subject.

1) The youth of the patient Our youngest patient was 15, and the oldest 28.

2) Sudden onset, usually associated with physical exercise This occurred definitely in 3 of our patients The fourth was referred to sudden contact of the scrotum with cold water in a shower In the other 2 there was no distinct relationship to activity

3) Severe pain This was the usual situation, but one of our patients did not have enough to pain to report to the medical officer until 10 days after the onset

4) Absence of any history or evidence of genito urinary infection. This was true of all our cases except the first, where the diagnosis was obscured by the presence of pyuria, later found to be due to a hydronephrosis

5) The high position of the affected testicle, often with the epididymis anterior to the testicle The testicle was distinctly high in 5 of our patients, in only 1 of which could we palpate the *epididymis in an anterior position* In the others, tenderness and edema made localization impossible

6) Tenderness of the testicle was present in all six

7) Prehn's sign Elevation of the testicle increased the pain in all our patients, but it should be added that movement in any direction had the same effect

8) Edema of the scrotal skin was definitely found in 3 of our patients

9) Transillumination of the scrotum was impossible in any of our proven cases

10) Fever was present in 3 patients

11) Leukocytosis was present in all

Case 1 C E W , aged 23, was admitted on April 28, 1941, because of pain and swelling of the left side of the scrotum It had occurred 10 days previously, following some strenuous calisthenics, but had been rather mild and gradually progressive, until on admission the scrotum was quite large and tender He walked with some difficulty because of the pain when his thigh bumped the scrotum He gave no history of any kind of urinary infection His temperature was 100 2 F, pulse 92, and respirations 20

The physical examination was essentially normal except for the scrotum, the left side of which was swollen so that it measured 8 by 7 by 5 cm It was firm, tender, and nodular, especially along the posterior aspect The skin showed bluish discoloration and some edema Palpation of the spermatic cord revealed no deformity Any movement of the scrotum caused pain The prostate and seminal vesicles were normal to rectal examination

The urinalysis showed some mucus and 10 to 12 pus cells per high dry field Cultures showed Staphylococcus albus Tubercle bacilli were absent in stain and culture The red count was normal and there were 11,300 white cells, with 52 per cent polymorphonuclear neutrophils The Kahn test was negative Four days later the white count was 10,500 with 69 per cent polymorphonuclears

A tentative diagnosis of torsion was made on the basis of this history, though the mild pyuria and the nodular nature of the mass on its posterior aspect did suggest epididymitis He was given a 16 gm course of sulfathiazole before surgery with no benefit, except that the temperature did fall to 99 4 F

At operation a small hydrocele, containing 10 cc of blood stained, watery fluid was found An intravaginal type of torsion of the spermatic cord was present The testicle was markedly enlarged to 6 5 cm by 4 cm by 4 cm It was bluish black and obviously completely gangrenous. The hydrocele sac was thickened and edematous. A simple orchidectomy was done. Pathological study of the specimen confirmed the diagnosis of acute infarction of the testicle.

Postoperative course was uneventful until the seventh day when, while sitting in the barber's chair, he suddenly became quite dizzy and fainted. On recovery of consciousness and return to his bed he complained of retrosternal pain which he described as a "heavy" sensation associated with a feeling of asphyxia. He vomited and his pulse went up to 132 and the blood pressure dropped to 90. He responded to supportive treatment. Subsequent electrocardiographic studies suggested myocardial infarction, but the chief of the Medical Service felt that the findings were probably of extracardiac origin. A definite diagnosis was never made, but we have believed that it was probably a pulmonary embolism.

Two months later he was subjected to left nephrectomy for hydronephrosis secondary to atresia of the ureteropelvic junction. Recovery was uneventful.

The correct diagnosis was delayed in this case, partially at least due to the pyuria which was subsequently found to be from the hydronephrosis, but which led to an initial consideration of epididymitis as the diagnosis. The postoperative episode may have been a sequela which might have been avoided by earlier removal of the infarcted testicle.

Case 2. R. McQ., aged 15, was admitted in September 1941, with a complaint of pain in the left testicle. One-half hour after pedalling his bicycle up a steep hill, but while lying in bed resting, there was a sudden onset of severe, constant, aching pain in the left testicle. He vomited three times. He gave no history of previous genito-urinary disease nor of late descent or other abnormality of the left testicle.

The temperature, pulse, and respirations were normal. The physical examination was not remarkable except for the high position of the left testicle in the scrotum. Palpation or movement of any part of the left side of the scrotum caused considerable pain. The testicle was soft and not enlarged, but the epididymis was palpable anterior to the testicle and was firm and nodular. Movement of the testicle was exquisitely painful.

The urine was normal. The red count was 4,850,000, with 95 per cent hemoglobin. The white count was 20,850, with 81 per cent polymorphonuclear cells.

The patient was promptly taken to surgery. Within two minutes after the induction of nitrous oxide and ether anesthesia the torsion spontaneously disappeared. The scrotum was opened to reveal a small hydrocele containing about 6 cc of amber fluid. A twisted gangrenous appendix testis (hydatid of Morgagni) was removed. The testicle was bluish and tense, and the color did not improve after it was wrapped for 10 minutes in a warm, moist sponge. The mesorchium was short and narrow, leaving the upper half of the testis and the upper pole of the epididymis free within the hydrocele sac, and permitting the intravaginal type of torsion. An attempt was made to save the testicle, 4 or 5 slits being made in the tunica albuginea. A hydrocele excision was done and the lower pole of the testicle was anchored to the dependent portion of the scrotum.

His postoperative course was without event Six weeks later the testicle was firm and painless, but only about one-half normal size Unfortunately we were not able to see this boy again, but he illustrates how rapidly torsion of the spermatic cord may do irreparable damage to the testicle. The operation was completed within 6 hours of the onset of symptoms, but atrophy was the end result.

Case 3 H L W , a 22 year old corporal, entered the hospital on May 17, 1942, with pain and swelling of the left side of the scrotum Symptoms had first appeared in 1935, when he was awakened one morning with pain and swelling in that region He said that a small knot in the scrotum gradually increased in size to include the entire testicle After about 20 minutes the swelling entirely disappeared Again in 1937 he bumped the left testicle against the thigh, and this slight trauma was followed by swelling, pain, and tenderness in the scrotum The pain was severe for 2 or 3 hours, but disappeared entirely after 15 to 30 minutes flat on his back in bed In 1941 a similar episode occurred while swimming, but subsided with an opiate and 20 minutes in bed

The present attack followed immediately after lifting two heavy barracks bags The swelling reappeared in the left side of the scrotum This was painful only with scrotal movement At first there was a knot above and behind the upper pole of the testicle, which increased in size Bed rest, ice bag, elevation, and morphine gave no relief After 3 days he was hospitalized Admission temperature was 100 F, pulse 90, and respirations 20

There was a dusky red swelling of the left side of the scrotum with some edema The local temperature did not seem elevated The testicle was in the upper part of the scrotum and there was marked tenderness on the slightest manipulation The testiculo epididymal mass was somewhat larger than the right, but one could not delineate the component structures He gave no history of late descent of the testicle nor of unusual mobility

The urine was normal and the red count was 4,800,000, with 95 per cent hemoglobin The white blood count was 11,400, with 82 per cent polymorphonuclears

At surgery a completely gangrenous testicle and epididymis were found The fat about the upper end of the tunica vaginalis was gangrenous, and within the tunica was about 4 cc of slightly blood stained fluid The torsion was in the spermatic cord above the tunica, the extravaginal type A simple orchidectomy was done and recovery was without incident This was a case of recurrent torsion and clearly illustrates the possibility of saving a testicle by a fixation operation whenever the history and findings indicate that torsion has occurred When the patient comes to surgery only after a severe and prolonged episode the result may be the loss of testicle

Case 4 L G , a Negro soldier of 21, was admitted on February 25, 1943, with pain in the left testicle of 5 hours' duration which had followed contact of the scrotum with cold water in a shower He vomited 2 hours after the onset There was no history of urethral discharge nor of any kind of genito-urinary disease There was pain in the lower abdomen

Physical examination revealed a large, tense left testicle which seemed to be twisted on its longitudinal axis. A small, hard, very tender area was palpable on the posterior surface of the testicle. The blood and urine were normal.

He was operated upon 6 hours after the onset. Incision of the tunica vaginalis revealed a definite torsion of the testicle on a narrow mesorchium within the tunica vaginalis. The head of the epididymis was free and not attached posteriorly to the tunical sac. The torsion was reduced and warm saline sponges applied to the testicle. It regained a normal color and was then fixed in a proper position by plain sutures between the scrotum and the tough tissue at the lower pole of the testicle. He had a temperature of 100 F for the first 2 days, but his recovery otherwise was uneventful. Four months later there was no difference in size, consistency, or sensation in the two testicles. This was our most satisfactory result. The patient refused aspiration of the testicle to determine the vitality of the spermatozoa.

Case 5. M. S., aged 28, gave a typical history of recurring attacks of torsion, and was seen only as one of these attacks was subsiding. His first episode was at the age of 11, when he had a sudden attack of pain just above the left groin. He was unable to get out of bed and had difficulty moving the left thigh. The groin pain was sharp and accompanied by pain in the left testicle as well. There was some swelling in the groin and retraction of the scrotum on that side. All symptoms vanished after 2 or 3 days' use of alternating hot and cold packs. There were many recurrences, sometimes as often as every 2 weeks, occasionally involving the right testicle. With one testicle affected the mate would usually retract into the proximal part of the scrotum and relax only with the subsiding of symptoms. In each episode the pain was usually severe for about 24 hours, and between times there were no symptoms and no demonstrable abnormality. There was no history of urinary infection and repeated urinalyses were normal, as well as the prostatic secretion.

There was no constant inciting factor in these attacks. Some occurred while he was in bed and others followed some form of exercise. There was usually cramping pain on the involved side of the abdomen, but nausea, vomiting, or disturbance of bowel habits had not occurred. The swelling usually lasted 3 to 4 days, and the time could not be reduced by external pressure or by lying down.

On May 29, 1945 there had been an attack of pain on the left side followed by the usual swelling. It had persisted for 40 hours, but both pain and swelling were subsiding when he was admitted to the hospital.

There was a tender left hydrocele with an estimated capacity of 50 cc. It transilluminated well, and the testicle could be seen in the usual posterior position. There was no fever, and both blood count and urinalysis were normal. Within 6 days the swelling had almost subsided, and needle aspiration of the hydrocele obtained only 6 cc of clear fluid, which contained no pathological elements and was negative on culture.

Col. William H. Field, M.C., A.U.S., saw the patient frequently, and could find no evidence of hernia on either side. He was not explored for surgical fixation of the testicles because the war was ended, and he was being evacuated to the United States. The diagnosis must, therefore, remain presumptive.

Case 6 F W, aged 18, complained of a sudden onset of pain in the right testicle It came on while he was sitting quietly in a chair, about 15 minutes after he had returned from a 12 mile automobile ride After the onset the pain continued almost constant and only slightly relieved by lying very still, so that he was almost unable to sleep at night There had been no previous episodes and no history of any form of venereal or genito urinary disease He had been discharged from the Navy only 15 days previously and the urine and blood were found normal at that time His last sexual exposure, a month before, had not been followed by any symptoms of urethritis.

The family physician who saw the boy first made a tentative diagnosis of torsion The boy insisted on being sent to a large general hospital with a full time medical staff The urologist there insisted that the condition was epididymitis, and so informed the original doctor The patient then returned to his home, where he was hospitalized by the first doctor

Examination 2 days after the onset revealed that the right side of the scrotum was enlarged to about 1½ times the normal size and was somewhat reddened There was some edema of the skin and any movement caused severe pain He was apparently most comfortable lying quietly in bed, and elevation of the scrotum gave no relief. It was very tender and the structures could not be distinguished It did not transilluminate All laboratory work was normal, including the prostatic secretion, except for a white count of 13,600 Temperature was 99 F and pulse 82

At surgery an intravaginal torsion was found, with infarction of the testicle and epididymis The tunica vaginalis was unusually large, and extended high on the spermatic cord The testicle and the bulk of the epididymis were remarkably free within the sac and attached by a relatively narrow mesorchium which was twisted There was about 5 or 6 cc of slightly blood tinged fluid in the sac The torsion was clockwise The infarction made orchidectomy necessary

The left side of the scrotum was opened and an identical anatomical situation was found, with an unusually long spermatic cord also The parietal tunica vaginalis was excised and the testicle fixed to the scrotum

In this patient a correct diagnosis was made early by his family doctor only to be reversed by the urologist Operation was delayed 2 days and the testicle was lost, which might possibly have been saved if intervention had been earlier One who has made the same error in diagnosis can sympathize with the urologist

SUMMARY

Five proven and 1 presumptive case of torsion of the spermatic cord are reported Of the 5 proven cases, four were intravaginal and one extravaginal

Orchidectomy was necessary in 3 patients One testicle was saved but became atrophic later, while one apparently withstood the torsion without damage

In 1 case (the third) there were 3 previous episodes of what was undoubtedly torsion A fixation operation after one of these occasions would have avoided the removal of the testicle

The collapse of the first patient on the seventh postoperative day, with symptoms and findings suggestive of a pulmonary infarct, is a warning of the possible

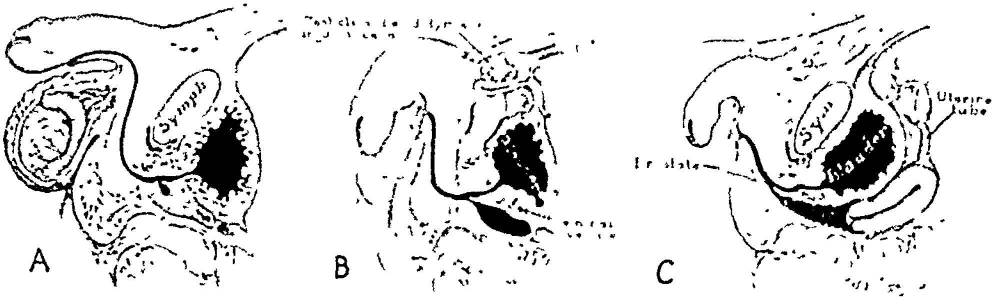

FIG. 1. From "Hypospadias with Enlargement of Prostatic Utricle," *Surgery, Gynecology and Obstetrics*, 86: 307–16, 1948. Courtesy of Dr. F. S. Howard.

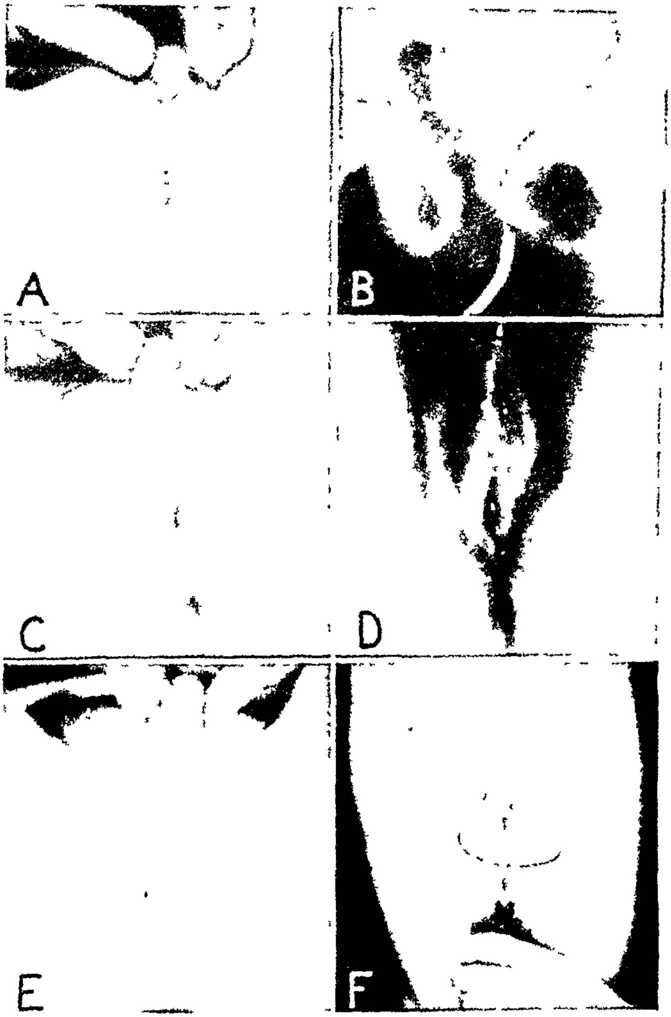

FIG. 2. Case 1, male pseudohermaphrodite. *A*, condition on admission. *B*, vaginogram. *C*, penis after straightening operation. *D*, showing urethra constructed from urogenital sinus to tip of penis (Thiersch operation). *E*, cure of male pseudohermaphroditism; urogenital sinus closed, urethra complete, vagina not excised. *F*, cure of male pseudohermaphroditism; normal urination, vagina not excised.

These findings are of great practical importance, because I think it shows that in male construction in hermaphroditism true or false, the vagina may be entirely disregarded and the urethra built first from the opening of the urogenital sinus to the end of the phallus, using the perineal opening of the urethra for drainage by a Foley catheter Suprapubic drainage is provided and then,

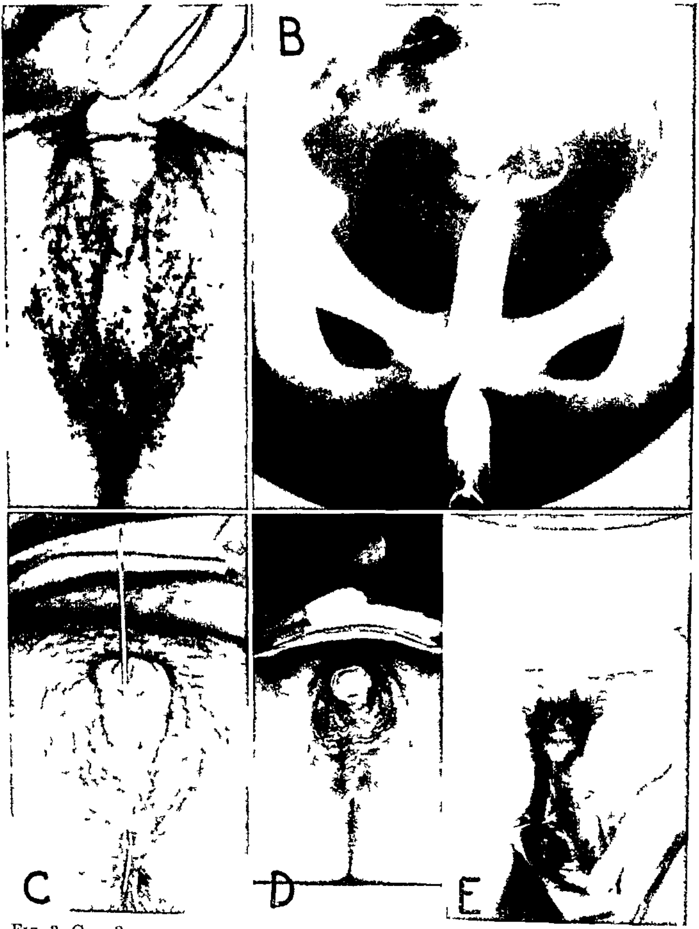

Fig 3 Case 2 [illegible] male construction A, penis has been straightened [illegible] thra from urogenital sinus to tip of penis (Thiersch [illegible] d, urethra complete, vagina not excised E, cure of [illegible] constructed, vagina not excised, normal urination

by an elliptical incision, the perineal outlet is closed The tissue depth is thick and offers no difficulties in closure I have done this unknowingly in other cases, but in the 2 cases that I am presenting today, this method was definitely planned

Figure 1, taken from Howard's article, illustrates that the greater the degree of hypospadias present, the greater the development of the vagina.

Figures 2 and 3 illustrate construction of the male urethra in hermaphroditism without excision of the vagina.

SUMMARY AND CONCLUSIONS

In the few cases of hermaphroditism heretofore reported, in which male construction has been done, it has been customary to excise the vagina. The only difference between male pseudohermaphroditism and perineal hypospadias is that in one the vagina has been discovered, and in the other it has not been discovered. It is present in both.

Hypospadias is of the nature of an intersex manifestation and not simply a failure of local coaptation. Since perfect results have been obtained in cases of perineal hypospadias in which the vagina was not known to be present and was not excised, it occurred to me that similarly good results could be obtained in hermaphroditism without excising the vagina as has been done heretofore.

Two cases with perfect urinary function are presented in proof of my theory.

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SECONDARY TESTICULAR TUMOR RESEMBLING KRUKENBERG TUMOR, A CASE REPORT[1]

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Secondary neoplasms constitute a very small percentage of all testicular tumors. Helfert and Pinck in 1944[2] reported the second case in the literature of secondary carcinoma of the testis from carcinoma of the prostate. These authors stated that less than 50 cases of metastatic tumors of the testis had been found in the literature to that date.

Bandler and Roen in 1946[3] reported a case of solitary testicular metastasis simulating a primary interstitial cell tumor of the testis. Two years after the orchidectomy in their case, hematuria developed and led to the removal of the right kidney. A routine intravenous pyelogram at the time of the previous orchidectomy was normal. Comparison of the renal tissue with the previously removed testicular tissue resulted in a final diagnosis of hypernephroid carcinoma of the right kidney with early solitary metastasis to the right testis.

Although not falling into the group of metastatic tumors of the testis, of sufficiently close relation is the report of Lewis, Goodwin and Randall[4] of a patient with carcinoma of the spermatic cord and epididymis extending from a carcinoma of the stomach. In this instance also the primary lesion was at first overlooked while attention was focused on the scrotal mass.

Another recent example of secondary testicular tumor has been reported in plasma cell myeloma of the spine (Kirshbaum).[5] Willis, in his recent textbook, *Pathology of Tumors* lists testicular metastases secondary to pulmonary carcinoma, melanoma of the skin and embryonic tumor of the kidney.[6]

The case to be described here is another in which orchidectomy was performed for an apparently primary tumor. The subsequent course proved it to have been a metastatic tumor.

CASE REPORT

M. J. M., a 38 year old veteran, had been in military service from July 1943 to September 1945. At the time of his induction into the army he had developed post-prandial epigastric pain. After extensive diagnostic studies in Army hospitals he was discharged with a diagnosis of a probable duodenal ulcer. The gastric distress continued after his return to civilian life. In 1946 (three years after the onset of symptoms) gastro intestinal roentgenograms showed a spastic duodenal cap. He continued to take various anti-acid drugs with moderate relief. In

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[1] Read at annual meeting, Western Section, American Urological Association, *Coronado*, Calif., January 17, 1949.

[2] J. Urol., 51: 635–640, 1944.

[3] J. Urol., 55: 663–669, 1946.

[4] J. Urol., 51: 75, 1944.

[5] Urol. & Cutan. Rev., 51: 456–459, 1947.

[6] St. Louis: C. V. Mosby Co., 1948.

September 1947 he first noticed a painless enlargement of the right testis. On December 17, 1947 he was referred to us because of increased swelling of the testis. He appeared thin and pale, the abdomen was flat, and no masses were palpable. There was a painless, hard swelling of the lower pole of the right testis and the overlying scrotal skin was adherent. The spermatic cord was also swollen, indurated and fixed. On rectal examination there was slight induration in the region of the right seminal vesicle. Laboratory tests showed a normal urine and a hemoglobin of 15 gm. per 100 cc. Serological tests for syphilis were negative. An upper gastro-intestinal roentgenogram made on December 15, 1947 was reported as normal except for a spastic duodenal bulb. A preoperative diagnosis of far advanced seminoma or embryonal carcinoma was made.

On December 22, 1947 a right orchidectomy was performed at the Cedars of Lebanon Hospital. The spermatic cord was divided at the internal inguinal ring. The operative wound healed readily and the patient left the hospital 1 week later. Following surgery his condition deteriorated rapidly. He developed abdominal distention, ascites, and symptoms of bowel obstruction. About 1 month after surgery it was found that the slight induration in the region of the seminal vesicle was now a very large, firm mass filling the cul-de-sac. Death occurred about 4 months postoperatively.

Pathological findings: The resected testis together with the adnexae and a segment of cord measured 10 by 4 by 3 cm. The testis itself made up only a small part of the entire mass. The parenchyma was firm and gelatinous and did not resemble that of normal testis. The thickened tunics, epididymis and cord were all indurated. Microscopic sections revealed testicular atrophy. Most of the tubules were represented only by a few Sertoli cells. There was increase of a poorly cellular interstitial stroma in which the Leydig cells were prominent. Here and there were nests and groups of neoplastic elements and occasional isolated cells. There was a faint attempt at acinar formation and some signet ring forms containing mucus. Similar elements invaded the thickened tunic in which mucinous pools containing neoplastic cells had formed.

Although an original diagnosis of an atypical embryonal carcinoma had been made, re-examination of the material prior to the patient's death led to consideration of the possibility that one was dealing with a metastatic mucinous adenocarcinoma from the gastro-intestinal tract, as in the so-called Krukenberg tumor of the ovary.

Autopsy findings (Dr. Grossman): The major findings at autopsy were in the gastro-intestinal tract. The intestines and omentum were plastered to the stomach and gallbladder in a packed mass. The wall of the stomach was enormously thickened and the rugae were prominent and tortuous. The thickening stopped rather abruptly at both esophageal and duodenal junctions. The sectioned surface of the gastric wall showed marked gelatinous swelling. From jejunum to rectum the intestinal wall showed the same thickening and induration as was seen in the stomach and which resulted in many focal areas of constriction. The gallbladder and appendix were similarly involved. In the ileum, small nodular mucosal masses were present, and there was a fungating and ulcerating mass 5 cm. in diameter in the anterior rectal wall. This was continuous with a mass of neoplastic tissue enveloping the prostate and seminal vesicles.

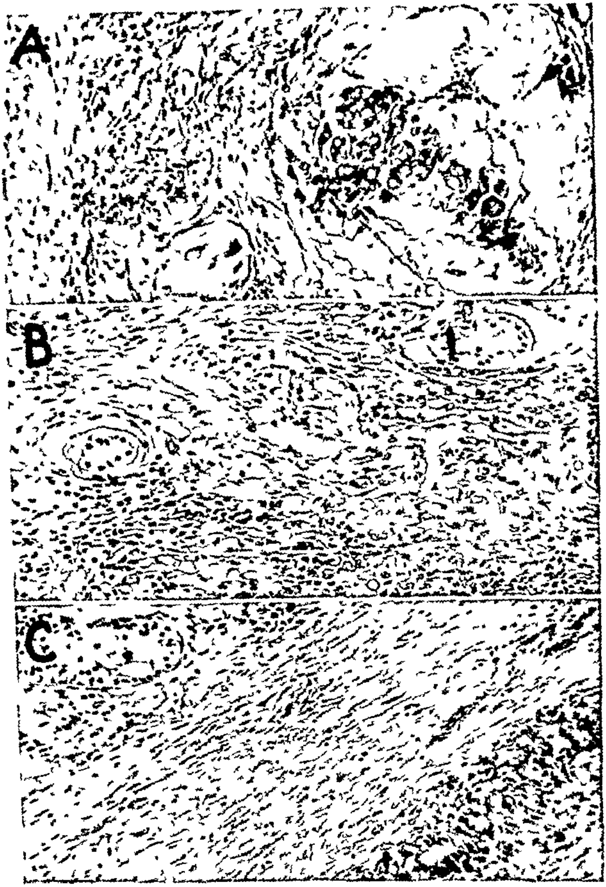

FIG 1 *A*, stomach wall, showing diffusely infiltrating adenocarcinoma Note signet cells *B*, testis showing infiltrating neoplastic cords A few atrophic tubules are present *C*, thickened tunica of testis with mucinous adenocarcinoma and pools of mucus

Microscopic study of the stomach revealed almost complete replacement of the mucosa by neoplastic growth composed of small uniform cells. Many were rounded, poor in cytoplasm and had a compact dark nucleus A few formed typical signet cells but mucus formation was the only real attempt at differentiation. The neoplastic tissue dipped deeply into the muscle coats and often extended into and along the serosa and subserosa. There was an accompanying inflammatory cellular reaction in the form of polymorphonuclear leukocytes, plasma cells and round cells. See figure 1.

The adherent fibrotic omentum was diffusely invaded by neoplastic cells. The duodenum revealed only an occasional small area of neoplasm but the jejunum, ileum, appendix and colon were as massively involved as was the stomach. The left testis revealed atrophy and moderate hyperplasia of the Leydig cells, but no tumor. The spermatic cord and scrotum were diffusely infiltrated by neoplastic tissue. In the operative field were foreign body granulomas in relation to sutures. There were metastases to the adrenal glands but not to the liver.

SUMMARY

The recent literature on metastatic testicular tumors is reviewed. In some of these cases the primary lesion was not evident and an initial diagnosis of primary testicular tumor was made. An additional case is reported in which the unusual points of interest are: 1) The diagnosis of "Krukenberg tumor" of the testis was suggested after reviewing the slides of the surgical specimen. 2) Although the patient had digestive disturbance for 5 years prior to death from gastric carcinoma and carcinomatosis, roentgenograms of the stomach 4 months prior to death were reported as showing only a spastic duodenal bulb.

These cases re-emphasize the importance of careful and thorough preoperative study in patients with testicular tumor.

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USE OF A BALL TRACTOR IN THE REPAIR OF VESICOVAGINAL FISTULA[1]

DUDLEY P. FAGERSTROM

The statistical results in the repair of vesicovaginal fistula present a challenge to the surgical profession, as evidenced by the number of patients still being subjected to multiple operations. Every unsuccessful attempt usually begets further trouble and increased likelihood of later failure, and a more scrupulous adherence to fundamental principles must be necessary before a single operative procedure becomes the rule, rather than the exception.

For many years the preponderance of such fistulas resulted from obstetric trauma, the abnormal ostium usually presenting in the lower portion of the vaginal wall. The burden of repair fell upon the gynecologist, who found the lesion easily accessible by vaginal approach. Currently, however, the great majority of vesicovaginal fistulas result from intrapelvic surgery or cervical radiation. Often the fistulous opening lies in close proximity to an intractile cervical stump, or in cases of previous total hysterectomy it may be involved in the dense scar of the pelvic floor. The upper third of the anterior vaginal wall lies in contact with the base of the bladder directly above the trigone, thus there is the possibility that the ureters may be incarcerated in the scar. Therefore in many instances the transvesical approach has many advantages over the vaginal route. Not only is the exposure of the operative site more adequate, but it facilitates liberation of the bound-down tissues and safeguards the patency of the lower ureters.

Preoperatively three cardinal principles demand attention: 1) elimination of infection in the involved tissues; 2) a thorough urologic study to determine a) the relation of the ureteral orifices to the margins of the fistula, b) damage to the upper urinary tract from incarceration of the ureter, and c) the presence of a complicating ureteral fistula; and finally 3) selection of an operative technique which carries the least possibility of recurrence.

THE TRACTOR

With the bladder opened, great difficulty has often been encountered in elevating the adherent bladder floor. The various types of hooks, screw tractors and forceps employed for this purpose have often proved more obstructive than beneficial. The tractor device which we are presenting is cheaply constructed and in our hands has proved of great value over the past 20 years. The ball is of solid sponge rubber with an outer surface of red shellac, measuring 3½ cm. in diameter, and of a type easily obtained at any ten cent store (fig. 1, *A*). A two feet length of No. 5 braided silk suture is passed through the ball and anchored in place with lead shot.

TECHNIQUE

After surgical preparation of the vagina, a sharply curved forceps carrying one end of the silk suture is introduced into the bladder through the fistulous opening. Through the opened bladder the suture is grasped and the forceps removed. As traction is made upon the suture an assistant slowly guides the ball into the depths of the vagina. Further traction on the thread will now often elevate the orifice of the fistula to the mid-plane of the bladder, the ball providing a firm, resilient support upon which cutting procedures are easily carried out. The traction remains in place throughout the entire repair procedure.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 17, 1949.

Primarily the rolled and scarred margin of the fistula is circumcised by sharp, right angle excision. The bladder muscle is now mobilized by undercutting the margin with an angled bistoury for a depth of 2 cm., or further if needed. It is essential that the coaptation of the bladder walls should be free from the slightest tension. The bladder and vaginal walls are now closed separately with chromic gut, the sutures avoiding the vaginal mucosa. No effort is made to close the layers in different planes. The bladder mucous membrane is tacked with fine plain gut, the traction thread cut flush with the suture line, the ball removed with traction through the vagina, and the bladder closed around a Pezzer catheter. See figure 1, *B*.

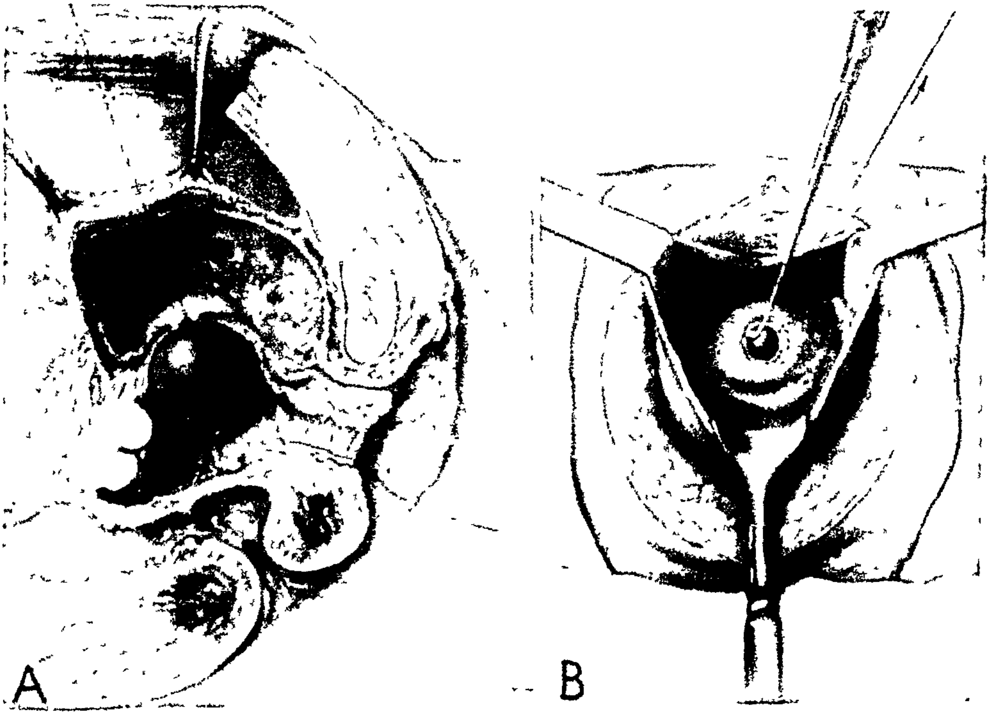

FIG. 1

The most essential postoperative precaution is to insure that the bladder remains empty at all times. Urine should not be permitted to lake upon the bladder floor. This may be prevented either by keeping the patient in the prone position during the healing period, or by supplementary urethral drainage through a 14 F latex Robinson catheter. We have employed both methods with equally satisfactory results.

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THE TREATMENT OF URINARY BLADDER DIVERTICULA BY MARSUPIALIZATION[1]

JAY J. CRANE

Marsupialization is defined as the operative formation of a pouch in the abdominal cavity in the treatment of cysts or other tumors. The term marsupialization, therefore, is used in attempting to describe a surgical procedure in the treatment of urinary bladder diverticula, which for any reason cannot be *totally* removed surgically, by transforming them into cysts with separate external openings. Later these cysts can be destroyed with a sclerosing medium.

In January 1940, I attempted to remove a vesical diverticulum whose capacity when viewed by cystogram was larger than the large bladder to which it was attached. The patient was classified as a poor surgical risk. The opening of the diverticulum into the bladder was beyond the trigone, densely adherent to all extravesical structures. The bladder neck was obstructed by a large trilobular hypertrophied prostate. It was evident that the diverticulum could not be removed, because of the adhesions surrounding it. The orifice of the diverticulum was entered with a pair of very long, curved forceps and manipulated until the tip could be palpated outside the bladder cavity extraperitoneally and well to the side of the midline. Then an incision through the skin and the abdominal wall was made down onto the tip of the forceps, which were extended out through the incision. The tip of a dePezzar catheter was grasped and pulled into the cavity of the diverticulum and anchored to the skin. The orifice of the diverticulum was resected from the bladder and closed with mattress sutures. The bladder opening was likewise closed. A suprapubic tube was introduced into the cystotomy wound. (See figures 1 and 2.) The patient was returned to bed with a suprapubic catheter in the bladder and a dePezzar catheter in the diverticulum, the diverticulum having been completely separated from the bladder.

The prostate was enucleated 8 weeks later, at which time the orifice of the diverticulum was found to be well healed. After the suprapubic incision was healed and patient was voiding normally, the diverticulum was irrigated by gravity with a measured amount of 10 per cent silver nitrate, which was neutralized later with sodium chloride. After a few weeks of such treatment the catheter in the diverticulum was removed and the sinus healed promptly.

I believed that it would be safe to remove the catheter from the diverticulum and permit the sinus to close, because I felt sure that if empyema of the diverticulum (cyst) developed, it would form a sinus to the skin at the site of the external opening into the diverticulum.

I have in private practice treated four such diverticula by this method, with thus far complete surgical cure in each instance. Two cases are illustrated in figures 3 and 4. I wish to recommend the procedure to any surgeon who is con-

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[1] Read at annual meeting Western Section, American Urological Association, Coronado, Calif., January 18, 1948.

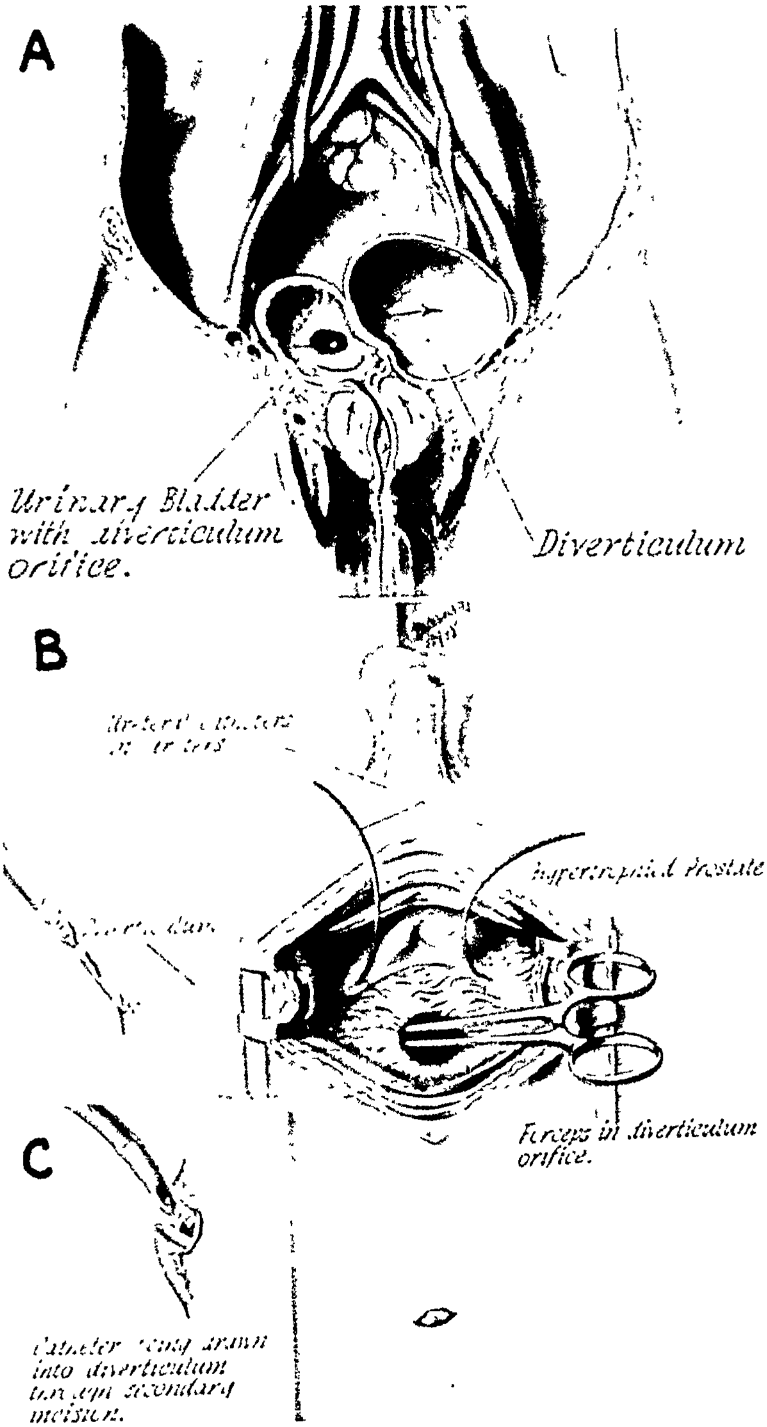
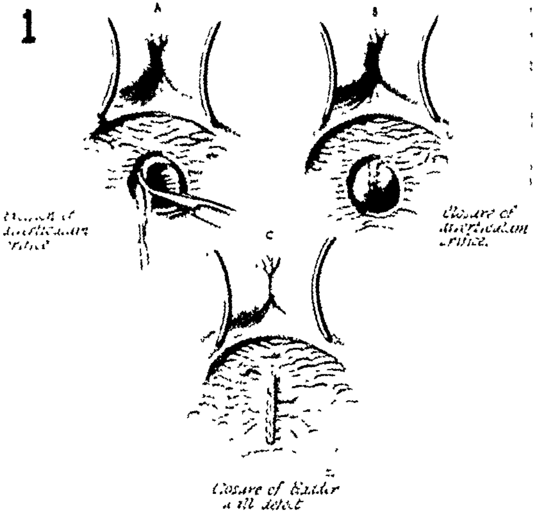

A
Urinary Bladder with diverticulum orifice.
Diverticulum
B
Ureteral catheters in ureters
Hypertrophied Prostate
Diverticulum
Forceps in diverticulum orifice.
C
Catheter being drawn into diverticulum through secondary incision.

Fig. 1

1


A
B
Closure of diverticulum orifice.
C
Closure of bladder wall defect

2

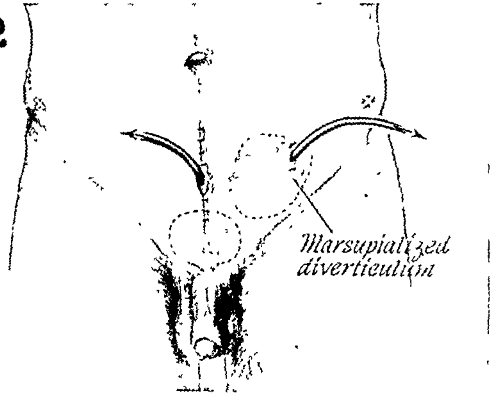

Marsupialized diverticulum

FIG. 2

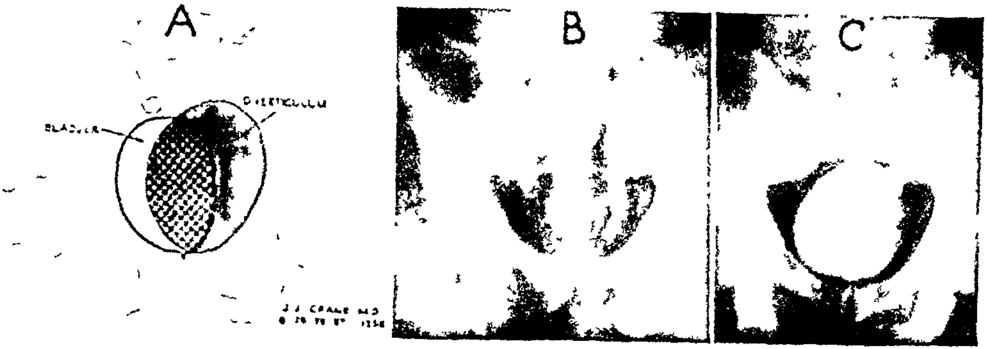


FIG. 3. Case 1. *A*, artist's interpretation of diverticulum of bladder from x-ray report. (Original film showing diverticulum was accidentally destroyed.) *B*, marsupialized diverticulum. *C*, cystogram taken after prostatectomy and destruction of marsupialized diverticulum, showing defect in left lateral wall of bladder where diverticulum was severed from bladder

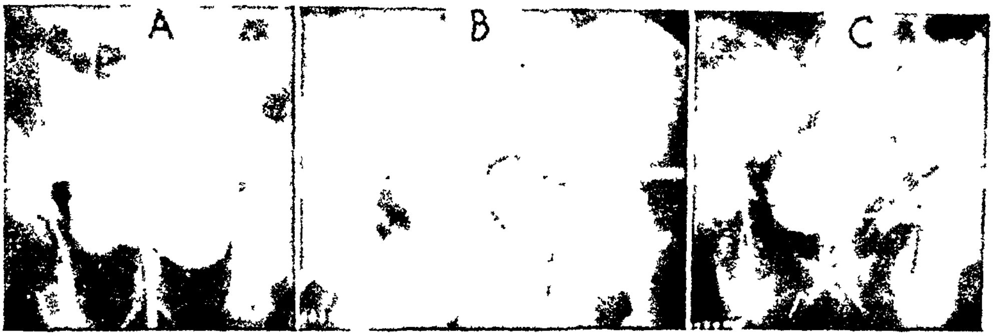


FIG. 4. Case 2. *A*, diverticulum of bladder before marsupialization and prostatectomy. *B*, marsupialized diverticulum at time that catheter was removed. *C*, cystogram after closure of marsupialized diverticulum and prostatectomy had been performed.

fronted with an infected, nondraining diverticulum of the bladder, which cannot be safely and entirely removed surgically.

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OCCULT PROSTATIC CARCINOMA DIAGNOSED UPON TRANSURETHRAL RESECTION[1]

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In a recent paper,[2] we presented statistical arguments showing that an average survival of 63 months (a 5 year survival of 56.5 per cent) favors radical surgery as the best form of treatment of prostatic carcinoma when the lesion is diagnosed early. But it also has been established that only about 5 per cent of all patients with carcinoma of the prostate are seen early enough to make the radical operation thus effective. Although this low percentage of early diagnosis is mainly due to the fact that few patients present themselves for examination while the lesion is still localized since carcinoma of this organ has an insidious onset, it is in part due to the inability of the examiner to detect early malignant changes on rectal palpation, because the tumor is not typically scirrhous or is not in the posterior portion of the gland which is accessible to the palpating finger. The magnitude of this latter source of error is greater than we previously had thought: whereas only 15 early cases had been diagnosed soon enough to be treated by radical prostato-seminal vesiculectomy at this clinic in the last 20 years, there were in this period 59 patients with early cancer in whom the diagnosis had been missed on rectal palpation (and on cystoscopic inspection as well).

In the 59 patients in whom the diagnosis of carcinoma had been missed on rectal palpation, cancer was discovered subsequently on routine study of tissue resected transurethrally in 27 and of the specimen removed on perineal or suprapubic enucleation in the other 32 cases. As a result of this finding, 9 of the former and 5 of the latter had radical prostatectomy on the assumption that such was evidence of an early diagnosis. Analysis of the 27 cases of carcinoma diagnosed first on transurethral resection is made with the purpose of determining whether resection provides a means of early diagnosis and could not prove to be a valuable adjunct to rectal palpation in diagnosis. Comparing the results in the 9 cases which received radical treatment after transurethral resection with those in the remaining 18 which did not, will give some indications for the urologist to follow upon the discovery of carcinoma at or after resection.

ANALYSIS

Although the present series is much too small for significance in statistical analysis, the average survival of 36.8 months of the early cases treated by transurethral resection alone (5 year series) can be roughly contrasted with our previous series[2] of early carcinoma treated by radical prostatectomy which had an average survival of 63 months. However, since presumably the carcinoma had progressed to a greater degree in the cases diagnosed on endoscopic resection (as most carcinomas progress from the true prostate into the peri-urethral adenomatous portion) strict comparison with so-called early cases in which the lesion feels rectally to be limited to the posterior lamella is not entirely justified. Included in this group are 4 cases in which only benign prostatic hypertrophy was found on the initial transurethral resection and carcinoma on the second, done 1, 37, 48 and 120 months later, and 2 cases in which only benign prostatic hypertrophy was discovered on perineal prostatectomy 2 and 10 years before the transurethral resection in which carcinoma was found. These cases are similar to those reported by Hunt[3] and Flynn.[4] The following case report is representative of the group treated by transurethral resection alone: P. H. F., 63 years old, entered the University of California Hospital on June 14, 1933 having had increasing difficulty emptying his bladder for 5 months, finally necessitating thrice daily self-catheterization. He was found to have a 1½ times enlarged gland, which was described as firm but not suspicious of carcinoma. Cystoscopy showed bilateral and commissural hypertrophy; consequently transurethral resection was done without carcinoma being suspected until the pathological report was received showing carcinoma of the prostate (fig. 1). The patient died 16 months later from widespread prostatic carcinoma.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 18, 1949.

[2] Hinman, F., Jr.: The early diagnosis and radical treatment of prostatic carcinoma. Calif. Med., 68: 338-343, 1948.

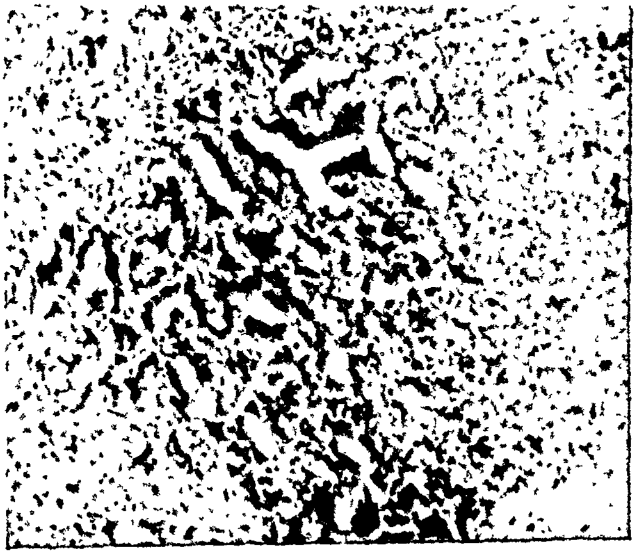

FIG. 1. Case 1. Photomicrograph, showing rather wildly growing strands of carcinoma in transurethral resection fragment.

In comparing the results of these patients with carcinoma treated by transurethral resection alone (table 1) with those in which the carcinoma was diagnosed by transurethral resection and then treated by radical prostato-seminal vesiculectomy, we find that whereas the average survival of those treated by transurethral resection only and followed 5 years of more (9 cases) was 36.8

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[3] Hunt, V. C.: Carcinoma of the prostate gland and prostatic capsule developing subsequent to prostatectomy for benign prostatic hypertrophy. J. Urol., 22: 351–362, 1929.

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months, that of those treated by transurethral resection plus radical prostatectomy (5 cases) was 67.8 months. This is better than 5 years, better than by any palliative measure. This comparison indicates that it is possible to perform radical prostatectomy with a chance of increasing survival even though the lesion has involved the peri-urethral adenomatous area. A case, typical of the group treated by radical perineal prostatectomy after transurethral resection, is presented:

TABLE 1. *Analysis of 27 cases of prostatic carcinoma diagnosed by transurethral resection*

	SERIES	NO CASES	AVERAGE SURVIVAL
Transurethral resection only	2 years or less	9	Series unclosed
	5 years	9	36.8 mos.
Transurethral resection plus radical perineal prostatectomy	2 years or less	4	Series unclosed
	5 years	5	67.8 mos.

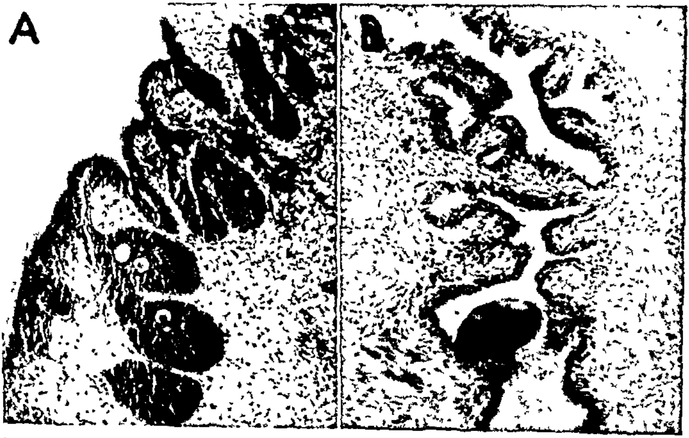

FIG 2 Case 2. *A*, low power view of inflammatory polyp resected on second examination *B*, *high power view of benign prostatic hypertrophy* Although initial transurethral resection fragments contained carcinoma, no carcinoma was found in portion removed by radical prostatectomy.

J. W. G. was 55 years old when he had the onset of symptoms of prostatism. This difficulty culminated 1½ years later in acute retention, and a transurethral resection was done. The sections showed carcinoma and he was admitted for possible radical surgery. His prostate was found to be slightly enlarged without areas of hardness. Cystoscopy and bilateral vasectomy were done and several polypoid nodules were seen anteriorly, on which the pathological report was "inflammatory polyps" (fig. 2, *A*). After radical prostato-seminal vesiculectomy, the pathological report was benign prostatic hypertrophy and chronic prostatitis (fig. 2, *B*) by Dr. J. Rinehart, pathologist: "I do not find anything that I can definitely classify as carcinoma. However, in the sections of the transurethral resection in this case prepared by Dr. Wood there is no question in my mind that there was one definite focus of carcinoma." Recent telephone conversations determined that this patient is symptom-free 8 years after his operation.

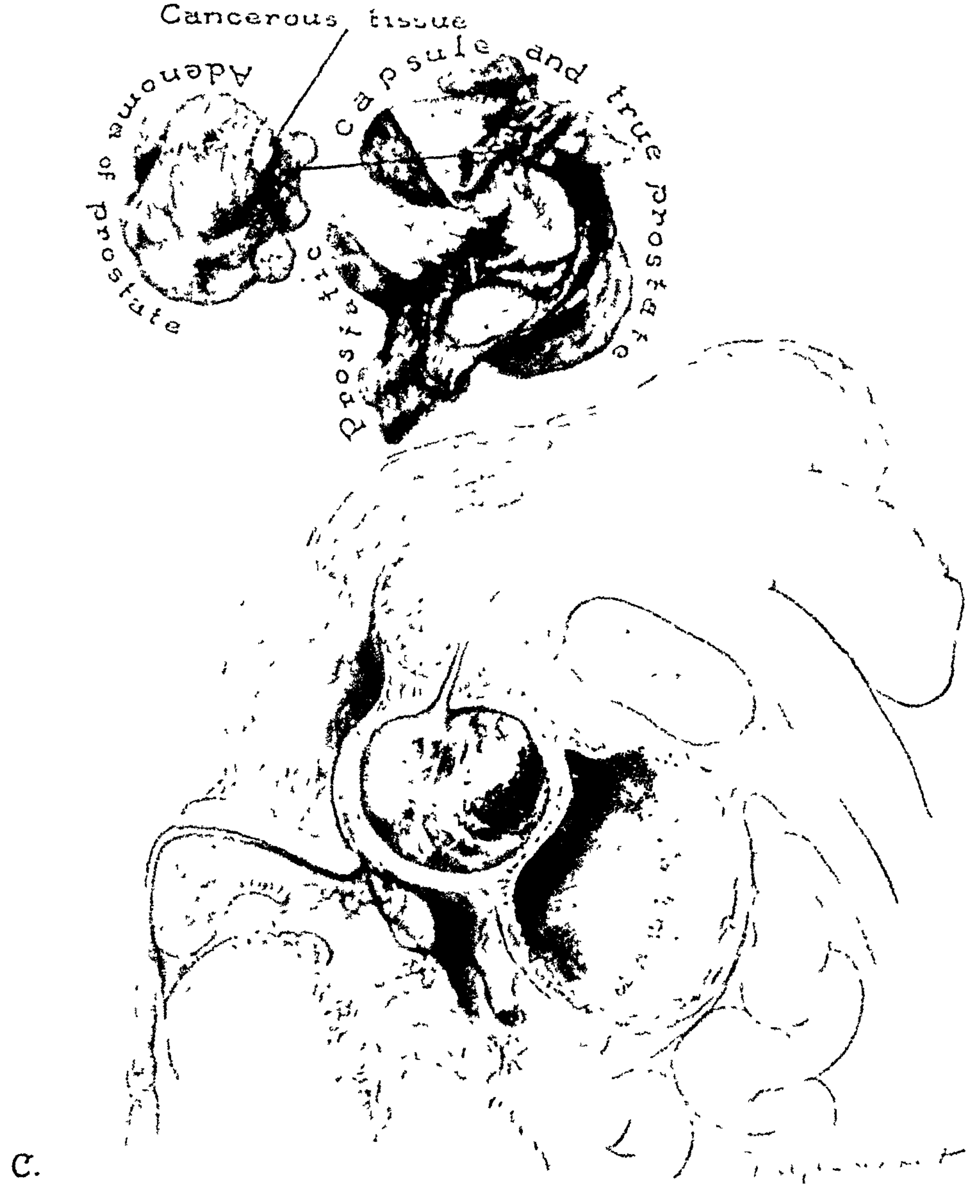

FIG. 3. Drawing of nodule of carcinoma (in a 68 year old man) found during intended simple perineal prostatectomy lying between adenoma and true prostate; radical prostatectomy then done.

Mention should be made of the remaining large group of partially analyzed cases in which carcinoma was found on perineal prostatectomy (25 cases) or on suprapubic prostatectomy (2 cases). The fact that the former group is much larger than the latter is merely a reflection of the relative frequency of the two types of operation at this clinic in the past and is not a measure of the admittedly greater frequency with which prostatic carcinoma can be exposed through the perineal route. The average survival of these patients was 44 months, only slightly better than that for transurethral resection alone. In five additional cases, a radical prostatectomy was done after carcinoma was found on perineal exposure for benign prostatic hypertrophy (fig. 3). The late results are not determinable because there was 1 operative death, 2 deaths from coronary thrombosis months after leaving the hospital and one suicide for reasons other than ill health. It is surprising that this group is so small for a 20-year series and would indicate that the importance of utilizing the perineal approach in exposing unsuspected prostatic carcinoma may have been overemphasized.

DISCUSSION

Occult carcinoma has been reported before[5–12] but the purpose of this analysis is essentially a practical one, for the urologist wants to know upon finding carcinoma in the fragments of tissue removed on transurethral resection whether or not radical perineal prostatectomy should be carried out. The answer to this question is not easily found. It was shown in the previous paper that the results of the radical operation were superior to palliative treatment. For the radical operation to be equally effective after transurethral resection it must be known that the growth has not yet extended beyond the capsule or metastasized, in other words, that it is still an early growth even though it has reached the periurethral region. Most of the evidence indicates that the carcinoma rarely originates in the adenomatous tissue[13–20]. If it did so more frequently it would be

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possible more frequently to remove the cancer completely with the fragments during transurethral resection. Since Shaw[9] in this country confirmed Albarran and Hallé[10] by his report of a case of early carcinoma arising in benign prostatic hypertrophy, several other reports have appeared confirming this source[6,7,11,18,21,22]. Some of these cases may be explained by growth into the adenoma from a primary focus in the true prostate as in the case shown, and in certain cases[23,24] this source was not ruled out by serial examination of the prostate. Some, however, are examples of true malignant change in a nodule of hypertrophy, such as Albarran and Hallé originally described. But even in the usual case in which carcinoma begins in the true prostate, it has been shown that it remains within the capsule until it has spread rather widely in the prostatic tissue, and that while perineural involvement occurs early within the surgical capsule, such spread outside is a rather late phenomenon.[11] It is desirable for the resectionist to use any or all of three means to detect small areas of carcinoma. The first of these is the use of semi-serial sections of all fragments removed[25]; this is tedious and expensive but is used as routine in some clinics. The second, and certainly less expensive, is the examination of many razor-cut sections of fresh tissue stained with methylene blue (Terry technique[26]) to allow selection of those fragments most likely to contain carcinoma on later permanent section. The third is the segregation of peri-urethral from capsular fragments by complete evacuation of the former before the final part of the resection is begun. Barnes, Bergman and Farley[27] found that they were able to diagnose carcinoma in 2.4 per cent more cases by this means than by the usual one of examination of random fragments.

Part of the answer too to this question comes from analysis of the result of such a procedure in our clinical experience. By comparison of patients in whom carcinoma was found on transurethral resection and no further operation was done (average survival, 5-year series, 36.8 months) with those in whom the initial discovery was followed by radical perineal prostatectomy (average survival, 5-year series, 67.8 months), it is seen that, although these figures are not statistically significant because of the small number of cases, they are suggestive of the results that may be expected.

CONCLUSIONS

If microscopic examination is made of suspicious fragments from transurethral resection (or of localized suspicious areas in adenomata removed by open opera-

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tion) and an apparently localized area of carcinoma is found, our evidence is that radical perineal prostatectomy offers a greater chance of cure and should be performed

SUMMARY

Fifty-nine cases of carcinoma of the prostate not suspected preoperatively and discovered on transurethral resection (27 cases) or open prostatectomy (32 cases) are analyzed

Eighteen patients who had carcinoma discovered on transurethral resection and no other surgery had an average survival of 36 8 months

These are compared with 9 patients who had carcinoma found on transurethral resection and on whom a radical perineal prostatectomy was done. This group had the best survival rate, those operated upon more than 5 years ago (5 patients) living on an average of at least 67 8 months following operation

The conclusion is reached that even though *carcinoma of the prostate originates in the true prostate, its presence in adenomatous tissue is not necessarily an indication that it has already spread outside the prostate* Hence radical perineal prostatectomy seems indicated if an apparently localized area of carcinoma is found either on transurethral resection or on open prostatectomy.

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ENDOSCOPIC IDENTIFICATION OF TISSUE DURING TRANSURETHRAL PROSTATIC RESECTION[1]

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The identification of tissue as seen through the resectoscope lens during transurethral prostatic resection is essential to accomplish a complete removal of the prostate and to avoid removing tissue which should be left. It is as important for the endoscopic surgeon to differentiate the various types of tissue which are seen through the resectoscope lens as it is for the abdominal surgeon to identify and differentiate the tissues which he exposes and handles.

In order to obtain a clear and distinct vision, it is necessary to place the inner end of the telescope very close to the tissue which is being examined and to allow the water to flow in to keep the field of vision clear (fig. 1). If the inner end of the lens is as much as 1 cm. away from the tissue which is being examined, it is very difficult, if not impossible, to identify this tissue. The closer the lens is to the tissue, the more magnification there is and the more easily this tissue is identified.

When beginning a transurethral resection, the first tissue removed is that situated at the bladder neck, and if the prostate is not very large in that region, bladder neck fibers are exposed after one or two excursions of the resectoscope loop. These fibers are easily identified and are seen as parallel, rather coarse, fibrous strands which lie immediately external to the bladder (fig. 2, *A*). It is very important to recognize these bladder neck fibers, for the resection should not be carried any deeper at this point and the loop should never be placed proximal to them. To avoid carrying the resection too high on the trigone and into the bladder, the resectoscope loop should be placed distal to these bladder neck fibers at the beginning of each subsequent excursion of the loop.

The resected surface of prostatic tissue can be easily differentiated from bladder neck fibers, for the former is granular, fuzzy in appearance, and softer than the fibrous tissue of the bladder neck (fig. 2, *B*). The true capsule of the prostate is however more difficult to differentiate from prostatic tissue than are bladder neck fibers, but by close observation a difference can be seen. The true capsule is fibrous in nature, and the tissue strands are finer than those of the bladder neck and interlace rather than being parallel with each other (fig. 2, *C*). The appearance is also smoother and more shiny than prostatic tissue. When the capsule is exposed over an area of 1 or 2 cm. there is an elastic sensation, or appearance, due to the elasticity of the capsule which is evident after prostatic tissue has been removed down to the capsule. If the resectoscope loop is pressed against this exposed capsule, the tissue is pushed away easily, and is not resistant. This is similar to the elasticity which is felt when the finger is in

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado Calif., January 17, 1949.

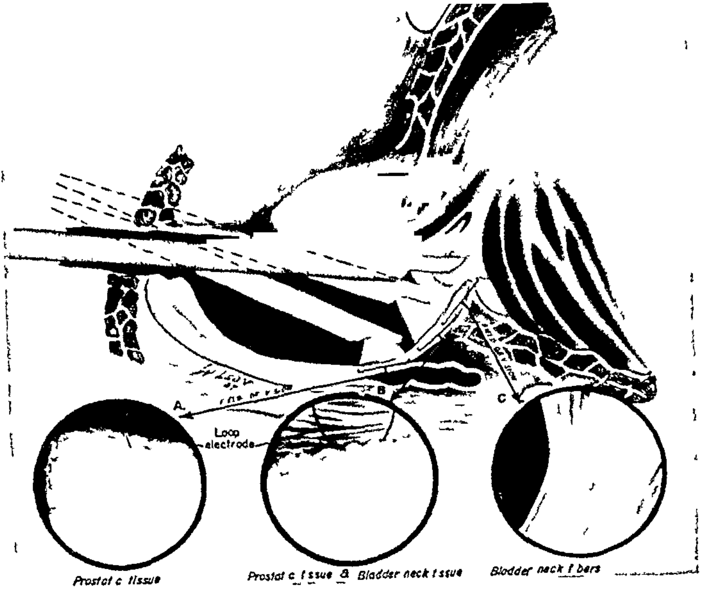

FIG 1 Inner lens of resectoscope placed near tissue to obtain adequate visualization

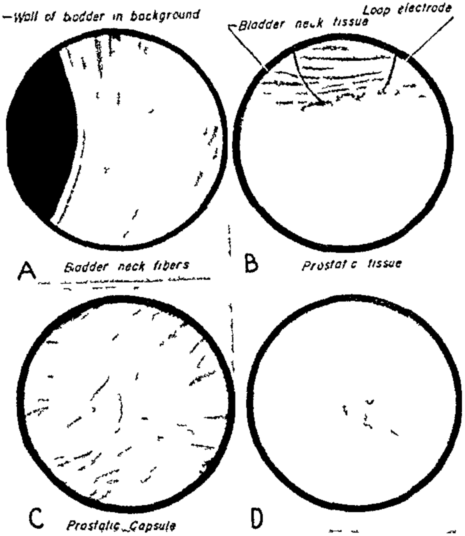

FIG 2 *A*, bladder neck fibers are seen as coarse, parallel strands of connective and muscle tissue *B*, prostatic tissue presents a granular or cotton like appearance *C*, true prostatic capsule consists of fine interwoven strands of connective tissue *D*, false or surgical capsule is firmer than hypertrophied prostatic tissue and often can not be differentiated from it

the rectum and the dorsal portion of the prostate has been removed down to the capsule.

Although it is not always possible to differentiate false or surgical capsule from hypertrophied prostatic tissue, in some instances this differentiation can be made. The false or surgical capsule consists of compressed prostatic tissue and the appearance is more solid and not so granular as hypertrophied prostatic tissue and more nearly approaches the appearance of true capsule (fig. 2, *D*). Theoretically it is possible to remove all of the surgical capsule down to the true capsule by transurethral resection, but practically this is seldom accomplished. On the other hand, by all methods of enucleation, the surgical capsule is always left, because the line of cleavage is between the adenomatous hypertrophy and the surgical capsule. Therefore from a theoretical standpoint, it is possible to accomplish a more complete removal of the gland by the transurethral route than by enucleation.

When the resection is carried into the true capsule, a near perforation occurs (fig. 3, *A*). It is important to recognize this possibility for the removal of another piece of tissue from such an area will result in a complete perforation and the danger of extravasation of irrigating fluid. The appearance of a near perforation is characteristic, the fibrous strands of the capsule stand out in relief and assume a crescent shaped appearance, and the deepest point is dark in color.

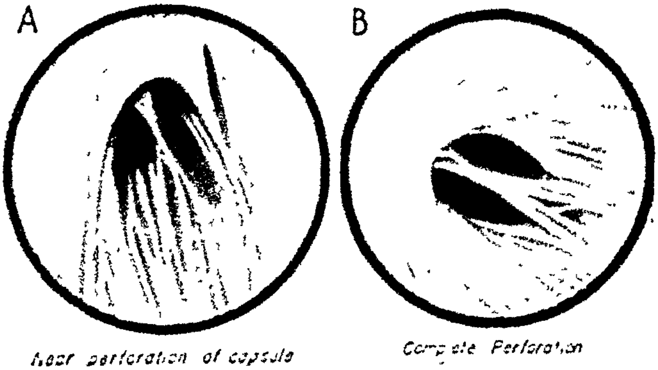

FIG. 3. *A*, near-perforation of capsule. *B*, complete perforation of capsule

A complete perforation of the capsule is very characteristic in appearance and it is extremely important that it be recognized as soon as it occurs. Spider-web like threads of tissue may be seen to stretch across a black area. If the perforation is very large, these threads may not be present. The edges of the perforation are formed by coarse fibrous strands of capsule, usually arranged in a crescent shaped or elliptical formation (fig. 3, *B*). The endoscopic surgeon who fails to recognize a perforation of the capsule as soon as it occurs subjects the patient to fluid extravasation and resulting shock. The characteristic suprapubic pain and rigidity which occurs when extravasation has taken place should never be a surprise to the operator, for the perforation should have been recognized through the resectoscope lens before sufficient amount of extravasation had occurred to produce these symptoms.

Neoplastic tissue of the prostate can nearly always be identified by its appearance through the resectoscope lens. When the carcinoma is very malignant, the tissue is much more fuzzy and soft than is hypertrophied prostatic tissue (fig. 4, *A*). When the neoplastic tissue is scirrhous in type and of a lower grade of malignancy, it is somewhat less granular and is firmer and more rigid than hypertrophied prostatic tissue. Occasionally a small area of neoplastic tissue, which is bright yellow in appearance, occurs as an islet surrounded by hypertrophied gland. Sometimes malignant tissue is identical in appearance to the normal or hypertrophied prostate and can not be differentiated from it. If during the course of a prostatic resection, the appearance suggests malignancy,

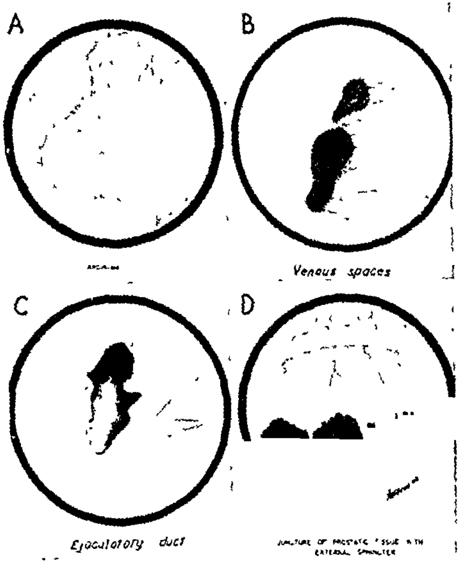

FIG. 4. *A*, carcinoma of prostate of high grade malignancy has a soft and fuzzy appearance *B*, appearance of venous spaces as seen through resectoscope. *C*, appearance of ejaculatory duct, as seen through resectoscope *D*, junction of prostatic with membranous urethra.

pieces of tissue should be saved from these areas for special biopsy study. Carcinoma occurs more frequently near the dorsal portion of the capsule than elsewhere in the gland.

Venous spaces appear as thin walled tubular structures which are usually collapsed and from which bleeding occurs continuously except when the bladder is distended (fig. 4, *B*). These are easily differentiated from a perforation of the capsule, for there are no distinct strands of fibrous tissue surrounding them. Sometimes a blood clot is seen to fill a venous space; it is therefore essential that overdistention of the bladder does not occur because of the danger of forcing these clots into the paravertebral venous system and producing emboli.

The ejaculatory ducts pass through the dorsal portion of the prostate near the capsule. These may be opened or cut across when the gland is being resected (fig. 4, *C*). They are tubular structures and are differentiated from venous spaces in that they are more regular in outline, they do not bleed, the walls are thicker, and they stand open rather than collapse. When exposed, they can be seen to be about ½ cm. apart in the floor of the prostatic urethra. It is probable that stricture of the ejaculatory ducts occurs when these structures are incised, and this might predispose to seminal vesiculitis.

The identification of the junction between the prostatic and the membranous urethra is important in order to avoid carrying the resection too far out with resultant injury to the external sphincter. Sometimes there is an accordian-like wrinkling of the mucosa at this point, which is more easily recognized when the resectoscope sheath is gently pushed inward after having been withdrawn so that the membranous urethra is visualized (fig. 4, *D*). This appearance however cannot be definitely relied upon to identify this point. The membranous urethra remains more concave than the prostatic portion throughout its entire circumference and when the hypertrophied prostatic tissue extends outward distal to the verumontanum, the encroachment of this hypertrophied tissue into the prostatic urethra can be visualized and differentiated from the evenly concave contour of the membranous urethra. The appearance of the tissue of the membranous urethra after it has been cut should not be relied upon to differentiate prostatic from membranous urethra, for if the resection is carried down deep enough to expose the muscle fibers of the external sphincter, sufficient damage has already been done to result in urinary incontinence.

In order to accomplish complete removal of the prostate during transurethral resection, the capsule should be exposed throughout the entire prostatic urethra. Palpation with the finger in the rectum and the resectoscope in the urethra is also an aid in determining whether or not all prostatic tissue has been removed. The latter maneuver does not, however, aid in identifying prostatic tissue which lies in the ventral portion of the prostatic urethra. For this reason, identification of capsule through the resectoscope lens is a more accurate method of determining whether or not all hypertrophied tissue has been removed than is palpation through the rectum. However, when both methods are used, the operator is more likely to remove the prostate entirely. It is, therefore, necessary that the surgeon be able to recognize prostatic capsule and to be able to differentiate it from prostatic tissue in order to accomplish complete removal of the gland.

SUMMARY

Identification of tissue through the resectoscope lens during a transurethral prostatic resection is as important as identification of tissue during open surgery. The granular appearance of normal or prostatic hypertrophied tissue, the coarse concentric bladder neck fibers, the interwoven fibers of the true capsule, and the softer fuzzy appearance of neoplastic tissue are differentiated. It is very important to identify near-perforation and complete perforation of the capsule

by the dark area surrounded by coarse fibrous tissue strands. The comparatively thick walled open tubular ejaculatory ducts are differentiated from the thin walled collapsible venous spaces. In order to recognize these differences, the lens of the resectoscope must be placed very close to the tissue which is being observed. A complete prostatectomy by transurethral method is almost impossible without identification of the prostatic capsule throughout the prostatic urethra.

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A CLINICAL COMPARISON OF THE USE OF GLUCOSE AND UREA IN IRRIGATING SOLUTIONS FOR TRANSURETHRAL PROSTATIC RESECTIONS[1]

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Urologists have long been searching for an ideal isosmotic, nonelectrolytic irrigating fluid to be used in transurethral resection of the prostate and in closed transurethral surgery on the bladder. The need for such a fluid was demonstrated to the author many years ago, when, at the hand of an expert, extravasation of distilled water into the perivesical space occurred, followed by shock, uremia, and death. This incident left an indelible impression and resulted in a determined effort to eliminate distilled water as an irrigating fluid. With the cooperation of Dr. Lucien Bavetta, biochemist, use was begun, in 1938, of 5.4 per cent glucose in distilled water; in 1946, 1.8 per cent urea was substituted for the glucose. The results of 8 years' clinical experience with glucose and 2½ years with urea irrigating solutions will be presented in this paper, particular attention being paid to six points of comparison.

I. PREPARATION OF SOLUTIONS

Both 5.4 per cent glucose and 1.8 per cent urea are isosmotic and nonelectrolytic. Both powders are pre-weighed, and autoclaved in sterile bottles or sterile paper containers, and this preweighed amount is added to a bottle of sterile, distilled water before operation is begun. Five gallons of solution, the amount usually used for a small resection, requires 1,080 gm. of glucose, but only 360 gm. of urea. In the beginning the regular 5 per cent glucose solution, in the 1000 cc vacoliter bottles which the hospitals provide, was used. However, private hospitals soon objected to this expense and it became necessary to furnish the glucose powder or sterile syrup and add it to the water at the hospital. To carry this larger amount of material is an added inconvenience to the procedure. The cost of glucose is three times that of urea.

Dissolution of urea is much quicker than that of glucose. In fact, urea dissolves endothermically, cooling the water down considerably; for that reason, it is wise to place a hot water bottle over the lower abdomen of the patient to heat the tubing through which the urea flows; this heat also serves to replace heat lost by the patient due to the irrigating fluid.

II. ADHESIVE QUALITIES OF SOLUTIONS

The glucose solution is somewhat sticky. Gloves and instruments become coated with the solution and it is necessary to wash them frequently. The urea solution does not have this adhesive quality and thus is more easily used by the operator.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 18, 1949.

III VISIBILITY

Vision, when glucose is used, is somewhat blurred because of yellowish haze on the lens caused by the adhesive property referred to previously Also glucose is nonhemolytic, so that red blood cells in small clumps may attach themselves to the lens, making it necessary to clean the lens, or change it, whenever vision becomes impaired

On the other hand, vision, when urea is used, is always clear Since 1 8 per cent urea is as hemolytic as water, very little clotting of blood occurs during operation, and for that reason good vision is always maintained This is a definite advantage since it facilitates resection

IV REACTION OF DIABETIC PATIENTS

It has been reported that after the use of glucose for resection in diabetic patients the blood sugar level has risen to such an extent that additional insulin is necessary The blood sugar level can easily be checked after the operation and the required amount of insulin added

Urea, however, does not affect the blood sugar level, nor alter the blood chemistry in any other way, thus eliminating any additional tests

V HEMOLYTIC REACTIONS

In 5 4 per cent solution, glucose causes no hemolysis During the use of glucose in the 8 years from 1938 to 1946, the reaction which has been described by Creevy and others with distilled water, was not observed Experiments in the laboratory have shown that glucose is non hemolytic in 5 4 per cent solution If this solution is decreased below 3 per cent, hemolysis begins to take place In this series, some patients had slight attacks of fever for 1 or 2 days, several had moderate chills, and a few had minor intestinal complaints such as nausea and vomiting which started during the operation and were attributed to the anesthetic or to other reasons beyond the control of the operator No cases of prolonged anemia or jaundice were encountered

In 1 8 per cent solution, urea is isosmotic but hemolytic However, in the laboratory it was found that 0 8 per cent urea is almost isotonic Up to December 15, 1948, 1 8 per cent urea has been used in 295 cases A report of the results in the first 227 cases of this series was presented in the *Journal of Urology*, December 1948 In 1 8 per cent urea solution, the red blood cells hemolyzed to the same degree as by distilled water No case of toxic hemolysis has occurred in this series In the last 65 cases more attention has been paid to the possibility of toxic hemolytic reactions than in the earlier series It has been found that if the venous plexus is entered and fulguration requires a longer period of time than is normally necessary, and if the irrigation has to be rather brisk, especially to evacuate blood from the bladder, the hemolysis of blood as determined in the plasma is increased in direct proportion to the time necessary to control the bleeding Also hemolysis increases in direct proportion to the amount of irrigation necessary during the operation And finally, it is in direct proportion to the time necessary to apply traction with a 30 cc Foley catheter. Only 3 cases can be reported of these 65 in which extensive fulguration was done to stop venous bleeding, and large amounts of hemoglobin were found in the plasma 4 hours after operation. In 24 hours after operation the plasma was free of hemoglobin in each case. In these 3 cases, symptoms such as low abdominal pain, slight backache, mild nausea and elevation in temperature were present. Laboratory tests and clinical observation disclosed no increased anemia or jaundice. The highest estimate of the free plasma hemoglobin was somewhat over 600 mg. per cent. The urinary output has always been adequate or above normal.

Griffin believes that hemolysis caused by distilled water alone is not enough to cause death, and King agrees that there must be more than one factor to produce death. He states that lower nephron nephrosis is the result of severe shock caused by the combined reaction to anesthetic, hemorrhage, and intravascular hemolysis. Creevy says the same. He states: "If hemoglobinemia is severe it may damage the kidney by producing spasm of its vessels, by a direct toxic action and by the production of pigmented casts which plug the nephron." Our clinical evidence seems to point to the fact that hemolysis alone is not enough to cause a lower nephron nephrosis. I believe that not enough hemolyzed blood to do damage enters the kidney even under prolonged fulguration. However, it is believed that a sensitivity of certain patients, perhaps a reaction to the anesthesia with unnecessary stimulation of the splanchnic nerves, or an ineffective nerve block, will set up a chain of nerve stimuli sufficient to cause the phenomenon of shock similar to that of the crush syndrome. Also continuous irrigations with distilled water, especially in cases in which a small rent may be present in the capsule, can be regarded as an additional factor. No oliguria such as has been reported in the above mentioned papers in which distilled water was used, has been observed in our series in which 1.8 per cent urea was used. Urea may act as a catalyzer which would stimulate the passage of the dissolved hemoglobin through the tubules, especially since it is well known that urea has a diuretic action.

VI. EXTRAVASATION

In the series in which glucose was used, extravasations of fluid into the retrovesical space occurred in 2 cases. These were treated by suprapubic cystotomy, drainage, and control of any possible shock or ileus. Intake and output of fluids were carefully checked. Neither oliguria nor anuria developed, and both patients recovered. Operation was completed later.

In 295 cases in which 1.8 per cent urea was used extravasation occurred in five. In this series, clinic, charity and private cases were included and resections were done by any member of the Group. Four of these patients, reported in the paper previously mentioned, recovered uneventfully. They were treated by cystotomy and drainage, and completion of the operation at a later date. The fifth case was almost the last of this series. It is worth reporting, since the patient was a poor surgical risk who suffered two complications during operation but recovered completely and left the hospital in an ambulatory state.

CASE REPORT

The patient (J. B., aged 73) was admitted to the hospital because of complete urinary retention. He was anemic, emaciated, disoriented and apparently uremic. The blood pressure was 180/90, the heart was not enlarged, and the lung findings were normal. The prostate was moderately enlarged. On catheterization, 450 cc of urine were obtained. The nonprotein nitrogen level of the blood was 51 mg. per cent; in the phenolsulphonphthalein test only 15 per cent of the dye appeared in 2 hours, none in the first 15 minutes. The urea clearance was 15.8 per cent of normal. The red blood cell count was 3,300,000. Transfusion and intravenous fluids, to make up for the amount he was not able to take up to 3,000 cc daily, were given. His intake and output seemed to be adequate. However, his irritability and mental confusion did not clear. At times he was able to talk but he became increasingly restless. After 1 week of drainage the nonprotein nitrogen level dropped to only 47.5 mg. per cent, the red blood cell count had increased to 3,700,000 and it was believed that a resection could be done. Following administration of spinal anesthetic his blood pressure began to drop. The operation was carried out rather rapidly in order to get the patient back to his room as quickly as possible. Toward the end of the resection, however, a rent must have occurred somewhere at the bladder neck because he became very restless and a tumefaction was felt in the lower abdomen. All arterial bleeders were quickly fulgurated, using as little irrigating fluid as possible. A Foley catheter was inserted into the bladder. A small, transverse, suprapubic incision was made, the fascia opened, and two Penrose drains placed on each side of the bladder. These permitted the drainage of large amounts of clear fluid, proving that extravasation had occurred.

The patient was taken back to his room in a satisfactory condition and supportive treatment continued. Four hours following the operation his blood pressure fell to 70/40, and he went into coma. A transfusion was given at once, oxygen was given by mask and 10 cc aqueous solution of adrenal cortex was added to the infusion. His blood pressure rose to 100/60. His urinary output during the first 24 hours was 1,460 cc. Twenty-four hours following operation he had a chill and his blood pressure fell to 35/0. Stimulation with adrenal cortex and caffeine was again employed, followed at once by 500 cc of whole blood given intravenously. Oxygen was continued. He responded well to this treatment; the blood pressure rose to 110/60. His nonprotein nitrogen level at that time was, 122 mg. per cent, the carbon dioxide combining power was 39 vol. per cent, plasma chlorides were 510 mg., the red blood cell count was 4,000,000. Neosynephrin in 0.5 cc doses helped to elevate his blood pressure to 140/80. The second day his urine output was 3,700 cc., the third day 3,400 cc, and the fourth day 2,300 cc. He received 1,200 cc fluids above his output. He also received penicillin and streptomycin. From the second day on, his blood pressure gradually rose, finally reaching its preoperative level. The urine cleared and the suprapubic drains were removed after 5 days. His coma cleared on the third day and oxygen was discontinued. The patient was able to take adequate liquids by mouth on the fifth day, and began to eat on the sixth day, at which time his catheter was removed and he began to urinate freely. The nonprotein nitrogen level 2 weeks following operation was 31 mg. per cent, his red blood cell count was 4,800,000 and his fluid exchange was adequate. The patient became less restless and more cooperative. He was discharged from the hosptal 2 weeks after operation, in an ambulatory condition.

I believe that the shock was caused by the poor physical condition and reaction to the anesthetic and sedation, not by the extravasation, and that the use of the urea solution instead of distilled water as the irrigating fluid played an important role in the patient's survival.

The extravasation of distilled water into the perivesical space seems to be followed by a series of events which throws some light on the mechanism of shock production in the crush syndrome as described by Bywater. When the distilled water penetrates the perivesical space, the patient usually complains of pain. This is followed by a state of shock, the severity of which depends upon the length of time the distilled water is in contact with the tissues, how much fluid extravasates and how high it dissects itself along the psoas sheath to the diaphragm. The patient sure to die is the one in whom the effect of the water is visible as far as the kidney and diaphragm. It can be deduced that the water causes an edema around the nerve fibers of the splanchnic nerves and the renal plexus, which can be compared to ischemia of the renal cortex produced by direct chemical stimulation of these nerve fibers as described by Trueta. Whether extravasation occurs on both sides depends on the locality of the rent. The chances of recovery seem less if both sides are filled with the distilled water. Water seems to result in a quick withdrawal of electrolytes from the tissue, which neutralizes the osmotic difference so that a collagenous material results. When isosmotic urea was used we never saw this collagenous fluid. This urea solution may be balanced sufficiently to prevent a chemical irritation should enough enter the perivesical space to extend along the psoas sheath to the kidneys and splanchnic nerves.

In our present series of cases, 0.9 per cent urea is being used. This solution is almost isotonic but only half isosmotic. The resections done with this isotonic urea to date have shown no hemolysis, and no extravasation has so far occurred.

SUMMARY

Eight years' experience with 5.4 per cent glucose and 2½ years with 1.8 per cent urea as irrigating solutions in transurethral prostatic resections have been compared. Extravasation of the irrigating fluid occurred in a total of 7 cases but no fatality occurred. Glucose is somewhat sticky to use but is nonhemolytic. No toxic hemolytic reaction resulting in death occurred in either series, although a mild temporary hemolytic reaction, from which the patient recovered completely, was noted with the use of urea. Because of this hemolytic reaction with 1.8 per cent urea, 0.9 per cent urea is now being used. This solution is almost isotonic to the red blood cells. The results of this series will be reported at a later date.

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SOLITARY HYDROCALYX SECONDARY TO A DUMBBELL CALCULUS[1,2]

JOHN W. DORSEY

"Hydrocalyx" is the dilatation of a renal calyx, secondary to obstruction existing in the infundibulum of the involved calyx. The infundibular obstruction may be produced by a primary calyceal calculus; or may result from the constriction of scar tissue secondary to a localized infection, with or without calculus formation. Adynamic factors have been stressed by Braasch. In the case described by K. H. Watkins, achalasia of the ring muscle of Disse was considered as a possible factor in the obstruction occurring at the junction of the infundibulum with the renal pelvis.

In reviewing the literature it was noted that there were few cases of true hydrocalyx described, and none identical with this case. The term "hydrocalyx" has been erroneously applied to associated renal changes. The nomenclature has been confused by various authors in discussing hydrocalyx; solitary renal cyst; parapelvic renal cyst; pyelogenic renal cyst (calyceal diverticulum); and obliterating pyelonephritis. None of the terms are in Dorland's dictionary except renal cyst. The diagrammatic sketch (fig. 1) illustrates these various conditions.

Solitary renal cysts occur in the cortex, and are of congenital origin. They do not connect with the renal pelvis, and their epithelial lining differs from that of the pelvis.

The term "parapelvic cyst" refers to those solitary renal cysts that lie in the renal substance adjacent to the pelvis, and when infected tend to rupture into the pelvis or a calyx. If rupture into the calyceal system occurs, they may be confused with pyelogenic cyst, but can be differentiated by study of epithelial lining. They may be identified on the basis that the lining epithelium is different from that of the calyx. Such a case was reported by Ridlon.

Pyelogenic renal cyst (calyceal diverticulum) is of congenital origin. The cavity containing urine is peripheral or distal to the calyx, and connects with it by a narrow isthmus. The involved calyx as a rule shows little, if any, evidence of obstructive uropathy. The epithelial lining of the cyst is continuous with that of the calyx. In establishing the diagnosis the delayed retrograde pyelogram will often show retention of the contrast medium in the cyst. This condition was first described by Par P. Rayor in 1841. The case reported by H. P. Winsbury-White in 1939 under the term "hydrocalycosis" appears from the illustration to be a pyelogenic cyst. Quinby and Bright report 1 case in which the capacity of the pyelogenic cyst was 1500 cc, whereas Holm says they are always of small size.

In localized obliterating pyelonephritis, as described by Hyams and Kenyon, the infundibular portion of the kidney may be the seat of an inflammatory

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[2] Dr. Dorsey's paper received the annual Joseph F. McCarthy Prize Essay award. *Editor.*

process which results in the destruction of the calyx, or by the production of a cicatricial barrier, in its isolation from the renal pelvis. These authors note that "obliterative infundibular changes as described may resemble, but should not be confused with, hydrocalyx, calyceal diverticulum, or similar lesions. The latter develop from congenital narrowing of the infundibulum in which, although calyceal dilatation may be progressive, the communication with the pelvis remains smooth and regular, in the absence of secondary infection or calculus formation."

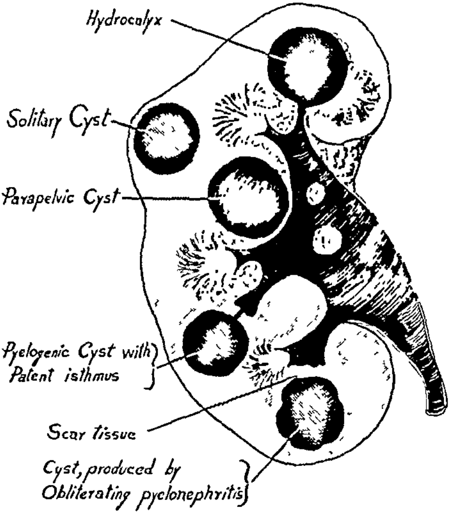
Hydrocalyx
Solitary Cyst
Parapelvic Cyst
Pyelogenic Cyst with Patent isthmus
Scar tissue
Cyst, produced by Obliterating pyelonephritis

FIG. 1. Schematic illustration of hydrocalyx; solitary cyst; parapelvic cyst; pyelogenic cyst with patent isthmus, cysto produced by obliterating pyelonephritis.

DIAGNOSIS

There are no characteristic symptoms. The patient may have a severe renal colic, dull flank pain, or be relatively asymptomatic. The diagnosis is established by roentgenologic urography. In the event of complete obstruction of the hydrocalyx it may be impossible to differentiate it from a large solitary renal cyst or neoplasm.

TREATMENT

The management of solitary hydrocalyx is governed by its size, symptomatology, location, and associated attendant renal pathological changes. A small hydrocalyx producing but few symptoms may be followed by serial urograms; and if not progressive, does not require surgical intervention. Hydrocalyx involving a superior major calyx may be drained by means of an indwelling ureteral catheter, introduced cystoscopically with relief of symptoms, as demonstrated by Beneventi. Lower and Belcher performed a heminephrectomy in their case with preservation of the remaining tissue. Caulk, in a similar case, made a nephrotomy incision; and under direct vision resected the scarred infundibulum. A nephrostomy tube was then introduced through the hydrocalyx and resected infundibulum to the renal pelvis. He reported a good result. O'Conor resected the dilated portion in 2 cases reported. These cases more closely resemble pyelogenic cysts. In the case reported nephrectomy was the procedure of choice, because of the attendant renal pathological changes.

CASE REPORT

A 28 year old white man, 12 hours prior to admission to hospital, developed suprapubic pain that became progressively more severe. Following the acute onset there was right flank pain, and a constant desire to void. There was no radiation of pain to the right testis or thigh; no chills, or gross hematuria. No history of previous similar attack or of genito-urinary disease.

Aside from slight tenderness elicited by percussion of the right costovertebral angle, and on deep palpation of the right hypochondrium and along the course of the right ureter, all physical and laboratory findings were negative. X-ray examination of the chest was negative for tuberculosis or metastases.

The plain urogram (fig. 2, *A*) revealed no significant bony abnormalities, and the psoas shadows were distinct. The right renal outline appeared larger than the left. Several small shadows of calcific density overlay the midportion and lower pole of the right renal outline; one appeared to be dumbbell shaped. There was a shadow of calcific density in the region of the terminal portion of the right ureter. The excretory urogram revealed good left and fair right concentration of the contrast medium. The left upper urinary tract was well visualized and showed no deviation from the normal. The right calyceal system was incompletely visualized, but revealed calycectasis of the superior and inferior group of calyces The calcific shadows appeared to be within the calyceal system. The right ureter was moderately dilated down to the level of the previously noted shadow of calcific density located in its terminal portion.

The observation cystoscopic findings were negative. Indigo carmine appeared from the left ureter in 4 minutes in excellent concentration, and from the right ureter in 6 minutes with poor concentration. A 6 F ureteral catheter was advanced 28 cm. to the right renal pelvis easily and 30 cc of urine aspirated. The culture of right renal urine revealed gram positive and gram negative bacilli. Smear for tubercle bacilli was negative. A urogram was then made using 30 cc of contrast medium, and withdrawing the catheter 15 cm. The ureteral catheter was then reintroduced into the renal pelvis and left indwelling to provide continuous drainage.

The superior and inferior group of calyces in the right retrograde pyelogram showed evidence of advanced calycectasis more pronounced in the superior group (fig. 2, *B*). There was a pressure defect originating in the midportion of the kidney, displacing the superior and inferior group of calyces medially. In the central medial border of this defect a portion of a centrally placed calculus was apparent. The remainder of the calculus was obscured by the contrast medium in the renal pelvis. The remaining shadows of calcific density occupied positions in the inferior minor calyces. There was no visualization of a middle group of calyces. The ureter remained dilated down to the level of the partially obstructing ureteral calculus located in its terminal position.

The ureteral catheter was removed 72 hours following its introduction and 2 days later the ureteral calculus passed and was recovered in the voided urine.

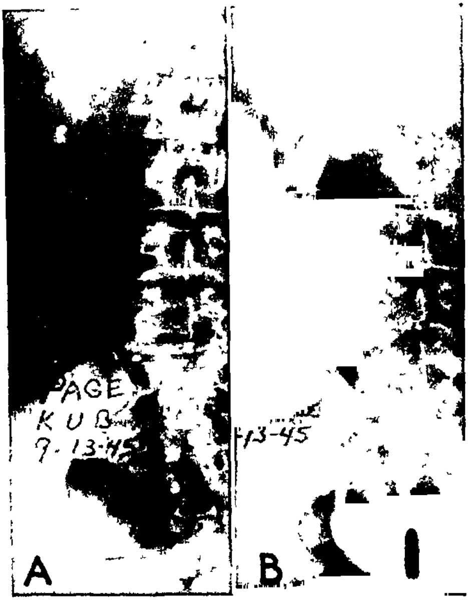

FIG. 2. *A*, plain urogram, showing hour-glass calculus in midportion of kidney, and multiple calculi in the lower pole Calculus overlying terminal portion of right ureter. *B*, right retrograde ureteropyelogram· Pressure defect in midportion of right kidney. Hour-glass calculus partially visualized.

During this period the peak temperature was 101.0 F, and his general condition appeared satisfactory.

Impression: 1) Right ureteral calculus; 2) multiple renal calculi; 3) chronic right pyelonephritis with calyectasis; 4) hydrocalyx, midportion right kidney; 5) the possibility of right renal neoplasm, solitary cyst, or tuberculosis must be considered.

Operation: Nephrectomy. A right lumbar extraperitoneal approach was utilized. The twelfth dorsal nerve was isolated and retracted posteriorly. The kidney was then mobilized without difficulty. The ureter was isolated, ligated, severed and carbolized. The renal pedicle was doubly ligated and severed. Two

Penrose drains were placed in the depths of the wound, and the incision was closed in layers with a running No. 2 chromic suture. The skin edges were approximated with clips. The immediate postoperative condition was excellent and he was discharged on the fourteenth day.

The gross specimen was an enlarged kidney (fig. 3, *A*). Projecting from the outer border was a tense, fluctuant tumefaction covering an area 7 cm. in diameter at the base and elevated above the surface 3 cm. Section through the area of tumefaction showed a cyst filled with clear fluid (fig. 3, *B*). This cyst was approximately 6 cm. in diameter; its wall was thin, but fibrous and trabeculated. The cyst communicated with the pelvis through an opening 3 mm. in diameter, which was completely occluded by a small calculus, dumbbell in shape, one extremity of which projected into the renal pelvis. The cyst was so placed that it obliterated the remaining middle minor calyces. The renal pelvis was slightly dilated. Over the surface of the cortex near the hilus were several small subcapsular nodules. A few of these were also embedded in the cortex and beneath this area was a dilated calyx which was ulcerated. There were several seed calculi and one larger calculus in the inferior calyces.

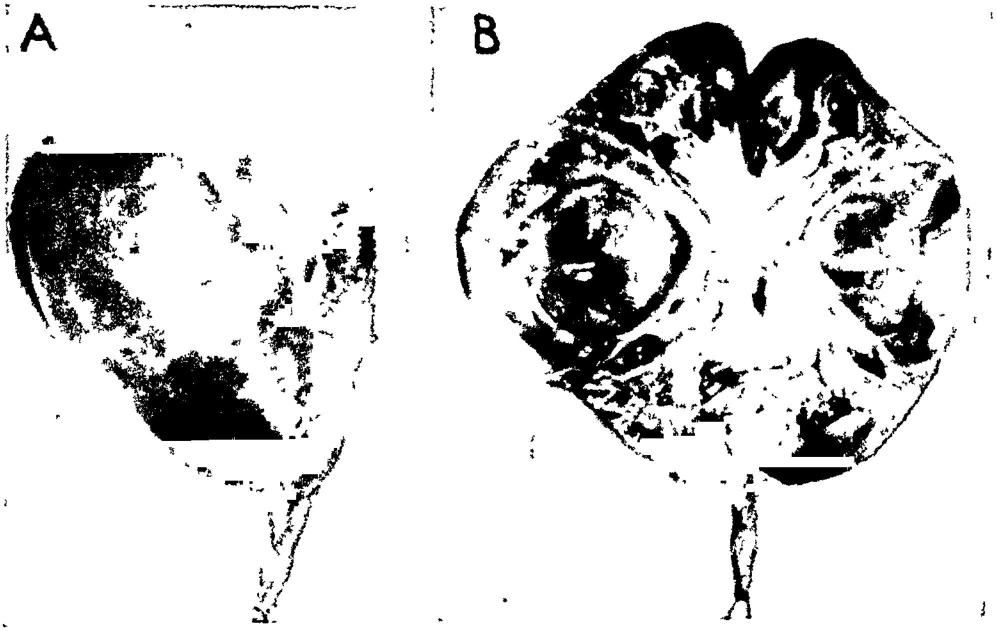

FIG. 3. *A*, gross specimen. Centrally located tumor mass. *B*, large centrally located hydrocalyx with obstructing hour-glass calculus partially visible. Calyceal necrosis apparent.

Microscopic examination of sections taken through different levels showed miliary abscesses, both acute and subacute in type. These correspond to the subcapsular and cortical nodules noted in the gross description. The cortex was diffusely infiltrated with lymphoid cells, plasma cells, and leukocytes. There was moderate tubular and glomerular necrosis. The lining of one of the calyces was ulcerated and the subjacent tissues were infiltrated by many inflammatory wandering cells. No evidence of tuberculosis was found. Diagnosis: Hydrocalyx, due to dumbbell shaped calculus, and pyonephrosis.

DISCUSSION

This case presents several interesting points for consideration. The extensive renal pathological changes were asymptomatic, the ureteral calculus initiating the acute onset of symptoms. A search of the literature discloses no other report in which a hydrocalyx of such size with its infundibulum completely obstructed by a dumbbell calculus. The filling defect created by the hydrocalyx was consistent with a large solitary cyst of the kidney, or a cortical renal neoplasm. The projection of a portion of the dumbbell calculus beyond the pelvis suggested the presence of a hydrocalyx, but inability to visualize the hydrocalyx precluded a positive preoperative diagnosis.

The question may arise as to whether the obstructing dumbbell calculus was of primary calyceal origin. The routine pathological sections failed to reveal the subepithelial calcifications first described by J. R. Caulk in 1912 and 1913, and later proven by the extensive investigation of A. Randall to be a common etiological factor in the production of primary renal calculi. It is regretted that serial sections were not made, in order to prove conclusively that this was a primary renal calculus. Herman has reported a similar defect secondary to stricture of the infundibulum. The associated major renal changes made nephrectomy mandatory in this case.

SUMMARY

A case of solitary hydrocalyx secondary to complete obstruction of the infundibulum is reported

No similar case was encountered in a review of the literature.

Differential diagnosis has been discussed.

There are no characteristic symptoms and the diagnosis must be established by roentgenologic studies and proven at operation

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ANOTHER CAUSE OF URINARY OBSTRUCTION[1]

H. M. PURCELL

I wish to present a case of urinary obstruction in the male caused by an anomaly of which I can find no record in medical literature.

A white man aged 54 years entered the hospital on February 29, 1948 with almost complete urinary retention. He first began to notice difficulty with starting his stream 5 years ago. The stream seemed smaller and was accompanied by aching in the suprapubic region. Nocturia began about the same time and had increased to 10 times a night with only small amounts at each voiding. Four days before admission he was unable to void but there was constant dribbling. A local physician attempted catheterization but was unsuccessful.

On reporting to the hospital, the doctor on duty catheterized him with some difficulty and obtained 900 cc urine which contained 1 plus pus and many bacilli. A Foley retention catheter was inserted.

There was a history of gonorrhea 25 years ago which was very mild with no symptoms of prostatic involvement. There had been no instrumentation of the urethra prior to the catheterization mentioned above.

A panendoscope was introduced with some difficulty in the region of the posterior urethra. The supramontane urethra was of normal length. There was no prominence of the prostatic bar, no lateral lobe prominence and no superior cleft. No valves were present and the verumontanum appeared normal. On withdrawing the panendoscope beak to the inframontane urethra, the irrigating water was shut off and this part of the urethra appeared normal. When irrigation was resumed two small openings could be seen on the roof of the urethra just proximal to the external sphincter. A probe introduced into the left opening entered only about ¼ inch. A probe in the right opening entered the bladder, the tip being visible but the opening into the bladder just out of the field of vision (fig. 1). A cystoscope was passed and very little trabeculation of the bladder wall was found and no hypertrophy of the trigone. There was no evidence of recent trauma to the anterior or posterior urethra. A 26 F sound was then passed to the bladder without resistance or hang. The prostate was normal on rectal palpation. Neurological examination was negative. The blood serology was negative and the nonprotein nitrogen was 17 mg.

Under low spinal anesthesia, a panendoscope was passed to the posterior urethra. An ureteral catheter, with a wire loop extending between the eyes of the catheter, was passed into the accessory canal and its floor incised to the bladder with the electric current, making a single channel of the posterior urethra. The edges of the other opening were fulgurated to obliterate this pocket. A Foley retention catheter was inserted for 24 hours. After removal of the catheter the patient voided freely. Six days later he was voiding easily with a good stream of

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 19, 1949.

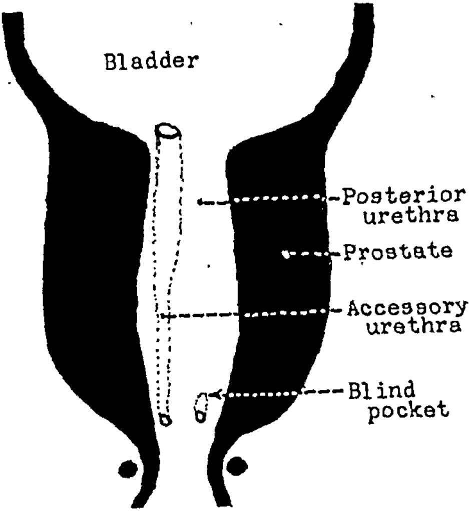

FIG. 1. Roof of posterior urethra showing accessory urethra and blind pocket.

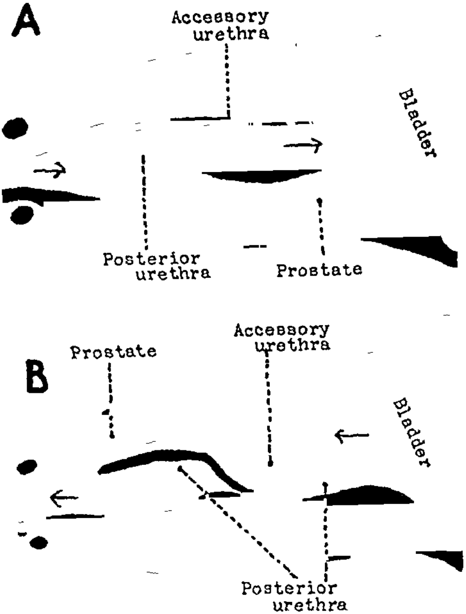

FIG. 2. *A*, vertical section through posterior urethra and accessory urethra, showing condition with irrigation water flowing through posterior urethra. *B*, vertical section through posterior urethra and accessory urethra, showing presumed condition on voiding.

clear urine and no residual. A communication from the patient 8 months later stated he was having no urinary difficulty.

Diagnosis: Accessory posterior urethra, producing acute urinary retention.

It is difficult to see how this deformity could produce the urinary retention, but it is presumed that the accessory channel ballooned out obstructing the posterior urethra (fig. 2). I believe this to be a congenital anomaly and have been unable to find a previous report of this condition.

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RENAL SARCOMA

REPORT OF A CASE WITH SPONTANEOUS RUPTURE OF THE KIDNEY[1]

TRACY O. POWELL AND JOSEPH E. CLARK

Sarcoma of the kidney, although uncommon, is always of pathologic interest. It has been estimated that only 2 or 3 per cent of primary malignant renal neoplasms in adults can be classified under this category. According to Bell[2] the great majority of renal tumors formerly classified as sarcoma have been found to be undifferentiated carcinomas. Excluding lymphosarcoma, there have been only 101 renal sarcomas reported in adults since 1910. It is our purpose, here, to report a case of renal sarcoma and to call attention to certain clinical as well as pathologic features of the disease.

CASE REPORT

Mr. P. F. B. (Hospital No. B95489), aged 53, was admitted to the hospital on March 22, 1947, complaining of severe pain in the left side of the abdomen of 48 hours' duration. The patient recalled a short episode of similar pain 3 months before admission and remarked that the lower part of his abdomen appeared "black and blue" for 1 week following this first episode of pain.

At physical examination a mild pallor of the skin and mucous membranes was noted. There was no discoloration of the abdominal wall; tense distention of the abdomen precluded palpation of any masses. A second glass specimen of urine contained 3 to 5 leukocytes and 2 to 5 erythrocytes per high power field. Study of the blood demonstrated 2,820,000 erythrocytes, hemoglobin 7.5 gm., and 14,100 leukocytes with 85 per cent polymorphonuclear leukocytes.

On the day of admission measures to relieve the distention were instituted; a barium enema study of the large bowel disclosed no striking abnormalities. The roentgenogram of the chest was normal. On the day following admission urologic consultation was sought. At cystoscopy the bladder was found to be normal and catheters were readily passed to each renal pelvis. Urine from each kidney showed only a few erythrocytes. Indigo carmine injected intravenously appeared in excellent concentration in five minutes from the right kidney, and in good concentration in seven and one half minutes from the left kidney. A plain roentgenogram showed a large left renal shadow (fig. 1, *A*). Retrograde pyelograms revealed elongation of the cephalad major calyx and depression of the middle major calyx in the left side (fig. 1, *B*). A diagnosis of tumor of the left kidney was made and preoperative preparatory measures were started.

Whole blood, 2000 cc, was given in units of 500 cc each.

Operation was performed on April 4, 1947. Under spinal anesthesia the left retroperitoneal area was exposed through a curved lumbar incision. The kidney was surrounded by dark, partially organized blood clot and was densely adherent to the peritoneum over its anterior surface. After difficult dissection, the renal pedicle was isolated, clamped, divided and double ligated. The ureter was ligated and divided, and the kidney was removed. Inspection of the renal fossa disclosed about 500 cc of dark, clotted blood extending superiorly under the diaphragm and across to the right side beneath the posterior peritoneum (fig. 2). The left adrenal gland appeared normal and no indurated tissue or nodules were palpated in the area. The space was irrigated with normal saline solution, and the incision closed in layers with drainage.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 17, 1949.

[2] Bell, E. T. Textbook of Pathology. Philadelphia: Lea & Febiger, 1947, p. 712.

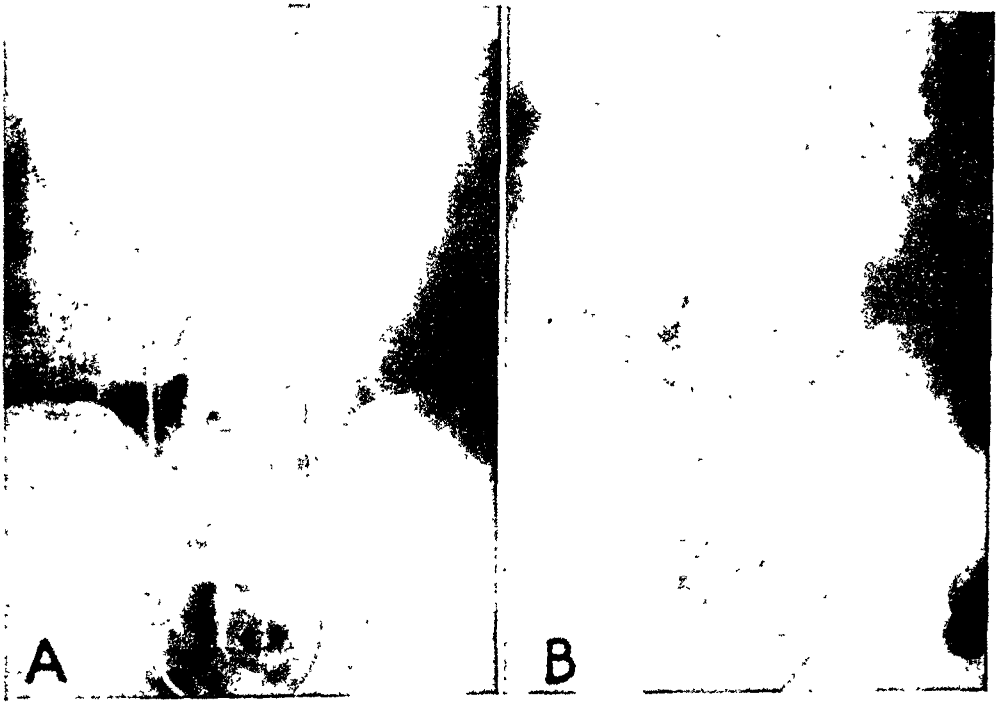

FIG. 1. *A*, plain x-ray, showing large left renal shadow. *B*, retrograde pyelo-ureterogram howing displacement of superior and middle minor and major calyces on left side.

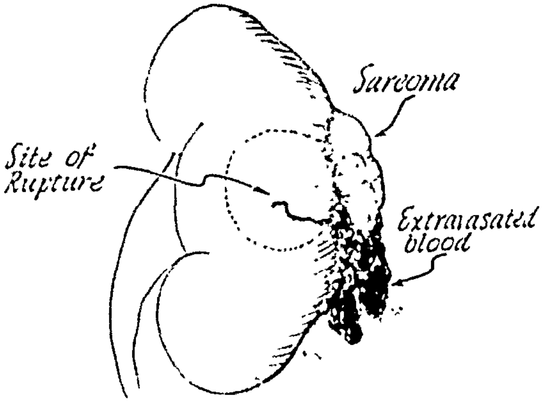

FIG. 2. External appearance of kidney at operation

The patient's course in the hospital was not remarkable, and he was discharged

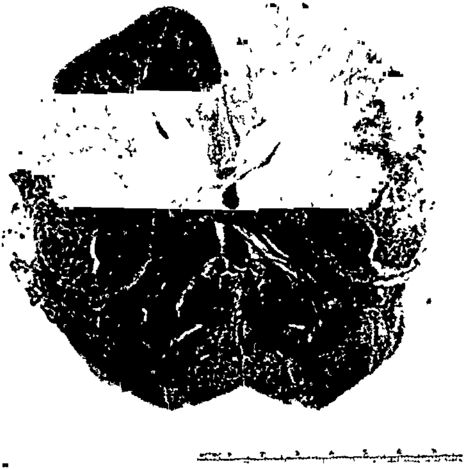

FIG. 3. Kidney after hemisection, showing large tumor between superior and middle major calyces, and small nodule in upper half of parenchyma adjacent to capsule.

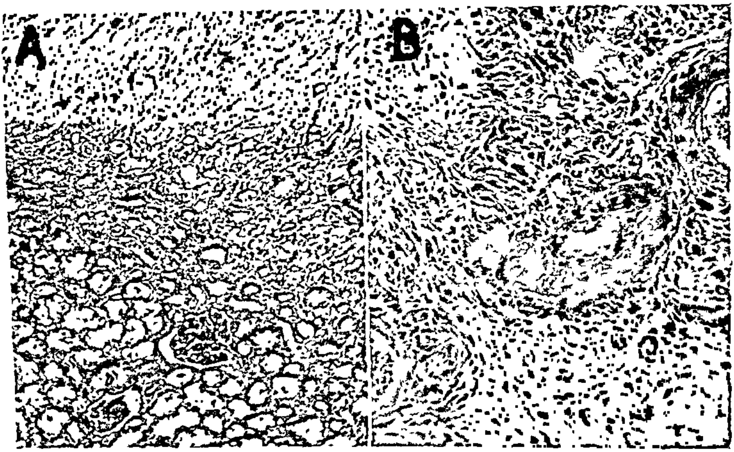

FIG. 4. *A*, showing normal renal parenchyma on left, and neoplastic replacement on right side. × 80 *B*, showing vascular area of tumor. Note thickened, hyaline vascular walls and short fibroblasts with dense nuclei. × 140.

on April 14, 1947. Postoperative follow-up to July 1948 has not discovered any evidence of metastasis or recurrence.

Inspection of the removed kidney revealed three small tumor nodules along the convex border and one larger, ragged area covered with blood clot just above midportion of the convex border. These tumors appeared to be sitting upon the surface of the kidney. After hemisection of the kidney, a tumor 5 cm. in diameter was disclosed within the parenchyma between the superior and middle major calyces. There was one small tumor nodule in the parenchyma of the upper half of the kidney (fig. 3).

Microscopic sections showed the two areas of renal tissue replaced by tumor composed of fibroblasts and spindle cells with whorl formation. The transition from normal renal parenchyma to neoplasm was abrupt, and there was no encapsulation of the tumor. Several areas of marked vascularity were apparent. The blood vessels exhibited thickened hyaline walls and there were many short fibroblasts with dense nuclei in these areas. The nuclei were fairly regular in appearance and mitotic figures were rare. The picture was that of fibrosarcoma (fig. 4, *A* and *B*).

DISCUSSION

Renal sarcoma, in most instances, appears during the middle years of life. Incidence between the sexes appears to be equal, differing from that of adenocarcinoma of the kidney in which 70 per cent of the tumors are in men.

There is no clinical feature diagnostic of renal sarcoma in the adult. However, it must be borne in mind that any tumor mass in the abdomen of a child should be thoroughly investigated as to the possibility of its being a Wilms' tumor (embryonal carcinosarcoma).

Many pathologists believe that the tumor originates from the renal capsule. This is logical, since the capsule is the site of greatest concentration of fibroblastic tissue in the kidney. A neoplasm developing in the region of the renal capsule must necessarily be extensive before it can invade the pelvis and calyceal system and produce blood in the urine. Such a theory fits the clinical observations in the majority of cases of sarcoma of the kidney. The sarcoma is found to be sitting on top of the kidney as might be expected of a tumor arising from the capsule—a feature possibly not emphasized sufficiently in the literature. We feel that this peculiar location and appearance of a tumor mass should lead to the strong suspicion that it is a sarcoma. Pyelographic studies from the reported cases would indicate that, in the majority, there are filling defects in the pelvis and calyces with irregularity of the parenchymal shadow, but a clue as to the unusual nature of the tumor is not in evidence.

The tumor is a yellowish solid mass which nearly always involves some portion of the renal capsule. Areas of hemorrhage are common. The microscopic pattern is variable, and confusion with other types of neoplasm, particulary undifferentiated adenocarcinoma, is always possible. A number of terms are used in attempting a descriptive diagnosis, but the majority of these tumors can be described as spindle cell sarcoma, fibrosarcoma, or as an embryonal mixed type.

Prognosis is poor regardless of type of treatment. Approximately 10 per cent of the patients may be expected to survive after the diagnosis is made for 5 years. This is much lower than the figures of 40 per cent for adenocarcinoma or hypernephroma and of 30 per cent for epithelioma of the renal pelvis.

SUMMARY

A case of renal sarcoma in an adult is reported in which there was spontaneous rupture of the kidney and pronounced retroperitoneal hemorrhage.

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EXPERIMENTAL STUDIES AND CLINICAL ASPECTS OF THE RENAL CIRCULATION[1]

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The elucidation of, and morphological studies on an intrarenal neurovascular shunting phenomenon by Trueta et al. in 1946–47 is one of the most significant contributions toward the correlation of anatomical, physiological and pathological data on renal function since Malpighii, Bowman and Claude Bernard. The work of Trueta that was the prelude to these findings began in 1941. At that time there was considerable concern about the anuria which often followed crushing limb injuries coincident with the London bombings.

A summation and correlation of many intensive, well-controlled, anatomical, radiological and physiological studies were published in monograph form in 1947 by Trueta. In view of this work a new concept was formed in regard to the pattern of the renal circulation. It was shown that the blood flowing through the kidneys has two routes which it may take, and depending on the particular conditions, may flow by one or the other of the routes. It also may flow through each simultaneously. These two "potential" routes involve cortical and medullary vascular circuits in the kidney (fig. 1). It was shown that this phenomenon by which the blood is shunted either into the cortex, or into the medulla (into the large juxta medullary glomeruli) is mediated through the nerve supply of the kidney.

With the evidence presented by Trueta that a double circulation existed in the kidney we started our work in an attempt to demonstrate these circulations. The purpose of our experiments is to show possible changes in the renal vascular pattern under the influence of varying degrees of hydration, and of certain drugs.

MATERIAL AND METHODS

The white female rabbit was the experimental animal used in this study. Intravenous nembutal anesthesia was used for all operative procedures.

To delineate the vascular pathway under either control or experimental conditions, India ink (Higgins) was injected into the marginal ear vein. In one type of experiment to be presented, it was impossible to administer the ink so that the gross appearance of the blood in the kidney gives the clue to the vascular pathways under consideration.

After the experimental procedures were completed and the animal killed by a sudden overdose of nembutal, the kidneys were removed and fixed in 10 per cent formalin.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 18, 1949.

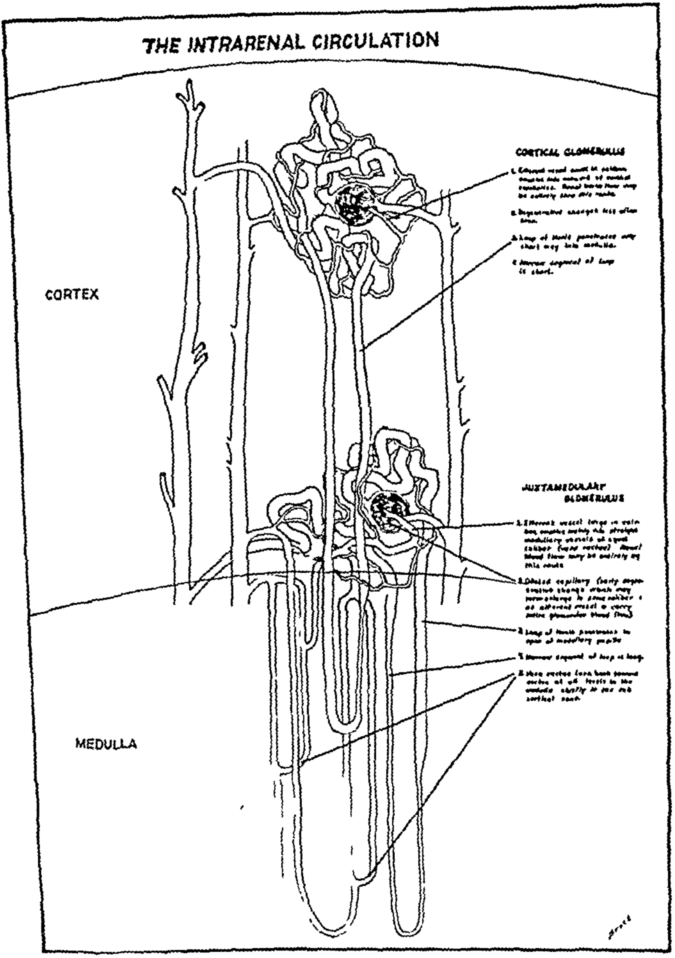

FIG 1

EXPERIMENTS AND RESULTS

A series of controls were run by anesthetizing animals (which were living under standard laboratory conditions) for a period varying from 10 minutes to 45 minutes and then injecting them with India ink. Figure 2, A shows the average *control kidney with a diffuse distribution of the ink throughout, and a slightly* lighter area in the medulla.

Another control series was run as above but without injecting the ink. Figure 2, *B* is the usual picture presented by the "normal" uninjected kidney.

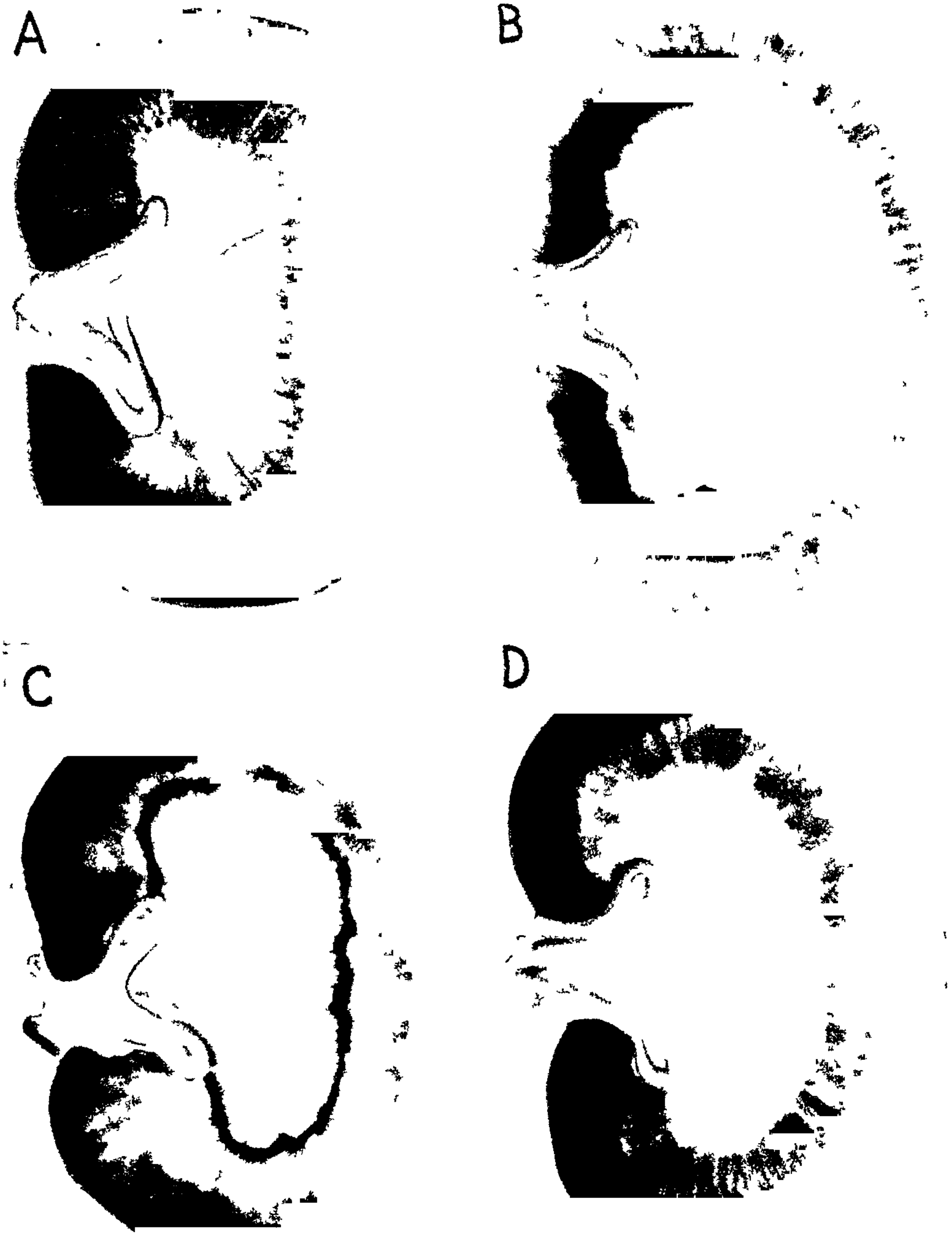

Fig. 2

To attempt to show the extremes of the two intrarenal circulation patterns several substances and methods were employed. Intravenous 1) pilocarpine and 2) magnesium sulfate were used, as were 3) water diuresis and 4) catharsis (producing dehydration).

The gross appearance of the kidney after intravenous pilocarpine is shown in figure 2, *C*. In comparing this specimen with the control, we can readily see the difference in vascular pattern as delineated by the India ink.

The effect of intravenous magnesium sulfate on the gross appearance of the renal vascular pattern is shown in figure 2, *D*. There is definite cortical concentration of the pigment.

Water diuresis produces what appears to be a more pronounced cortical concentration than does magnesium sulfate. Figure 3, *A* shows the small cortical rim produced by water diuresis. For the discussion to follow it should be pointed out here that the water diuresis produced was of very short duration.

Dehydration of the experimental animal was produced by severe catharsis (using Epsom salts, milk of magnesia, and Croton oil). In the absence of ink, the blood distribution in the kidney can be seen in figure 3, *B*. It shows a hyperemic medulla. This is a reversal of the findings in the other experimental procedures. This type experiment seems to indicate that the medullary circulation can be brought into action by dehydration of the animal.

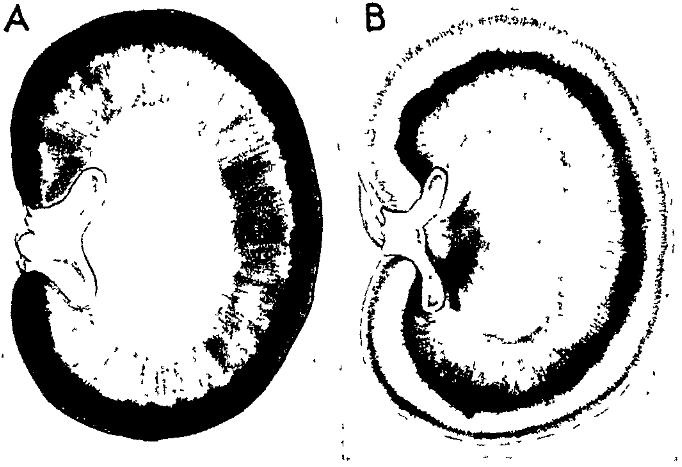

FIG. 3

DISCUSSION

The monumental work of Trueta and his associates, as well as that of many others which is now in progress, has thrown considerable light on the medullary circulation of the kidney. That two circulations exist and that the blood may flow almost entirely by one or by the other of these routes must still be borne in mind. The cortical circulation has been demonstrated most strikingly in our work by water diuresis and parenteral magnesium sulfate. The medullary circulation is demonstrable, we believe, by dehydration.

That this is only a preliminary report of our studies can not be too strongly mentioned. Therefore critical evaluation of these obvious changes in the intrarenal vascular pattern cannot be made until careful microscopic studies are completed and clearance studies are made.

The gross picture strongly suggests that the medullary circulation has been by-passed in water diuresis and partially by-passed (or at least altered the circulation considerably) by using pilocarpine and magnesium sulfate. Studies by Trueta, using x-ray methods, corroborate our experimental results with pilocarpine. Their work has shown that there was an increased shadow in the cortex and a decreased shadow in the medulla after pilocarpine had been administered. They believe that there is sufficient evidence to support the interpretation "that the increased cortical shadow is due to a dilatation of the cortical vessels . . . with a consequent reduction in the cortical speed of flow."

Trueta brought about an increase in the cortical shadow also by sectioning the splanchnic nerves, then applying a tourniquet in the thigh of the animal. The evidence then, that the cortical circulation can be separated from the medullary rests not only with our morphological studies but also with Trueta's radiographic studies. In addition we have shown that cortical concentration is brought about by magnesium sulfate, and most prominently by water diuresis.

That water diuresis causes cortical concentration of the blood is seemingly contradicted by the work of Ernst Frey. His studies suggest that in water diuresis there is a shunt of the blood to the medullary circulation. We believe, however, that our work is not actually contradictory, and in one set of experiments in reality corroborates Frey's work.

In reconciling the evidently diametrically opposite results of Frey's work and of our work, one should consider the reports of Gamble, Stewart and Rourke, and Wolf on water diuresis. These workers give good evidence that dehydration is produced by water administered over a long period of time. Wolf points out, in his studies on man, that after 3 hours of continuously administered water the urinary output was sustained at a constant level above that of the intake. It is evident then, that dehydration can take place with prolonged water ingestion. We suggest that the results obtained by Frey are those associated with the dehydration effect of the administration of water. The amounts of water and time over which they were used in Frey's study are not given, however in our studies diuresis had just begun when the India ink was injected and thus shows a different picture than that of Frey.

In our studies designed to demonstrate the effect of severe dehydration (i.e., by severe purgation) we believe the changes we found in the kidney are compatible with the picture described by Frey for his water diuresis.

The morphology of the kidney in our dehydration experiments is quite suggestively similar to that which is produced by stimulation of the renal nerves. We believe that the Trueta medullary shunt is produced by the dehydration of the organism.

There are certain clinical entities which we believe are manifestations of changes in the intrarenal circulation. Processes associated with ischemia of the cortical portion of the kidney are 1) bilateral cortical necrosis of pregnancy, and

2) alteration in the tubular system such as is frequently seen in lower nephron nephrosis. Ischemic changes in the region of the lesser circulation of the kidney are seen in necrotizing renal papillitis.

In all these phenomena vasospasm probably precedes thrombosis and the more permanent changes. The clinical aspects of these disease processes will be described more fully in a later publication.

We have presented preliminary studies on the effect of water diuresis, pilocarpine, magnesium sulfate, and dehydration on the intrarenal vascular pattern. Further microscopic, radiographic, injection, and clearance studies to elucidate the present findings are planned or under way. The suggestive significance of these early studies cannot be over-emphasized, but the fact that our evidence is, as yet, not unequivocal must still be kept in mind.

SUMMARY

A mechanism by which the renal blood flow may be altered has been demonstrated by Trueta, et al. (1947).

We emphasize the findings of Trueta that there exists a cortical and medullary route by which the blood may pass almost *exclusively by one or by the other*, depending on the circumstances.

In this work the blood was diverted almost exclusively into the cortical circuit by administration of pilocarpine, magnesium sulfate and most prominently by water diuresis.

The blood was diverted into the renal medullary circulation by dehydrating the animal.

The evidence for the above observations is not, as yet, unequivocal, but is still extremely suggestive.

Some clinical entities may be correlated with the changes in the intrarenal vascular pattern.

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RENAL HEMATURIA AND HYPOPROTHROMBINEMIA[1]

C. BALCOM MOORE

With the advance of urological knowledge the diagnosis of "essential" hematuria is decreasing, and fewer normal kidneys are being removed. Still smaller numbers may reach the pathologist when urologists come to recognize that such hematuria may be due to hypoprothrombinemia. The author's interest in this subject has been stimulated by seeing 2 patients with unilateral hematuria associated with low prothrombin blood levels. In neither of these patients could any cause for the hypoprothrombinemia be found, nor could any definite past or family history of bleeding be elicited.

In recent years there have been numerous case reports (Ershler and Blaisdell; Nelson and Washington; Richmond; Rosenbloom and Crane), and doubtless untold numbers of unreported instances of hematuria due to dicoumarol or heparin given for coronary thrombosis or phlebothrombosis. The bleeding is sometimes massive, even fatal, and often requires several transfusions for its control. However, there are only rare reports of hematuria as the first symptom of hypoprothrombinemia due to other causes. Nelson and Washington, reporting 3 cases of dicoumarol hematuria, advise the determination of the prothrombin time whenever the cause of hematuria seems doubtful, because they say that the patient may deliberately withhold the fact that dicoumarol has been given or may simply not associate it with the onset of his bleeding. They suggest that every patient be questioned as to drugs taken and that the prothrombin time be measured. The implication is that the urologist may be saved from a diagnosis of "essential" hematuria after doing a large number of expensive studies with negative results, or after having removed a kidney which the pathologist finds normal.

It has been known since 1904 that blood coagulates through the interaction of prothrombin, calcium ion, fibrinogen, and thrombokinase (or thromboplastin) the substance deficient in hemophiliacs. The first three are found in the plasma, the fourth is liberated by the breakdown of blood platelets or tissue cells, especially from the lung or brain. Owren's Factor V, which is discussed later, is probably one of several substances necessary for clotting which are normally present in laboratory preparations of thrombokinase made from rabbit lung but not from brain preparations (Quick).

Prothrombin is manufactured by the liver only with the aid of vitamin K, a substance present in leafy foods, eggs, and casein, and also produced by the colon bacillus, Staphylococcus aureus, bacillus subtilis, bacillus tuberculosis (Almquist, Pentler and Mecchi), and other bacteria. It cannot be absorbed if bile salts are not present in the intestine, which accounts for the hemorrhagic tendency in patients with obstructive jaundice, nor manufactured in sterilized intestines. Thus Collins and Hoffman report the case of a patient with hemoptysis and massive hematuria after using sulfasuxidine in the treatment of tropical sprue. Here they found the prothrombin time (Quick) to be 41 seconds, and stopped the bleeding within 3 days with vitamin K.

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[1] Read at annual meeting, Western Section, American Urological Association, Coronado, Calif., January 17, 1949.

The determination of prothrombin time by Quick's method is a measurement of the time required for clotting to take place in plasma containing an excess of calcium, after adding an excess of standard thrombokinase. It is, therefore, an indirect determination, which is subject to several variables, such as change in the activity of the thrombokinase, reduction in plasma fibrinogen, and unknown elements such as Owren's Factor V. To eliminate the first source of error the test is always done against a normal control, which in expert hands will give a reading of 11 to 12½ seconds, but may often reach 12 to 15 seconds. Errors, other than technical, are rare.

Howell's method for estimation of prothrombin time has now been abandoned because, being based on an inaccurate theory of the clotting mechanism, it does not, according to some authorities, really measure the prothrombin. It is mentioned here because the laboratory studies on my first patient were done by Howell's method, which has a normal value of 10 to 15 minutes.

Clotting time is a partial corollary of the prothrombin time and should be prolonged in marked prothrombin deficiency. In the capillary tube method whole blood is drawn into a tiny glass tube of uniform diameter and a small segment is broken off every minute until a clot is found. The normal time is 3 to 5 minutes. The Lee-White method determines the time required for clotting to occur in 3 small test tubes each containing 1 cc of blood. The first of these is tilted every minute until a clot forms, then the second, and finally the third. The total elapsed time (normally 4 to 10 minutes) from the moment of drawing or reconstituting the blood is the clotting time. The capillary tube method is almost useless for prothrombin estimation.

CASE REPORTS

Case 1. W. H., a white man, aged 40, an electric worker, was first seen on January 21, 1948. His illness began in July or August 1947, with painless pinkish 3-glass hematuria lasting for 2 or 3 days. His family doctor found some pus in the urine, administered a sulfonamide drug, and the hematuria stopped. About January 5, 1948, he noticed brownish-red opaque urine again. The next day he voided some small clots and another doctor advised rest and oral vitamin K for 4 days. About a week later, on January 14, an intravenous urogram was made and was interpreted by the roentgenologist as normal. On January 19, two weeks after the former attack of bleeding, the patient noted a recurrence of bleeding which was now continuous. During the time of bleeding there was slight frequency and nocturia, and mild strangury, but no other symptoms. There had been a slight sense of fatigue for the last 8 months, and he had lost 20 pounds, 8 of them in the last month. His present weight was 160. His past history gave no indication of a bleeding tendency, though he said his father had always seemed to bruise easily from slight trauma.

The patient was tall, muscular, somewhat emaciated, and his appearance suggested cancer. He looked 10 to 15 years older than his stated age. The blood pressure was 118/92. The liver was palpable 2 fingers below the costal margin in the right midclavicular line. It was smooth and not tender, and moved only slightly with respiration. The right kidney could be palpated when he was erect, and was normal size, somewhat irregular, and slightly tender. He voided 12 ounces of brownish-red urine in 4 glasses. The second glass urine had a specific gravity of 1.014, pH of 5.5, albumin 2 plus, no sugar, packed with red blood cells, 3 to 4 pus cells per field, and no bacteria on gram stain.

A review of the intravenous urograms taken the week before (January 14) showed a pear-shaped right kidney with the lower pole somewhat larger than the upper. The lower calyces were not clearly seen, but were apparently not abnormal. The upper pole of the left kidney was clearly seen, but the lower two-thirds was hidden by gas, and gave the impression of being about 3 times normal size. The upper and middle calyces were somewhat blunted, and the lower calyces seemed to be foreshortened and distorted. The left ureter deviated slightly toward the midline and was somewhat dilated down to the iliac artery. Function was good on both sides. The initial impression was carcinoma of the lower pole of the left kidney.

Cystoscopy was done the next day under topical anesthesia. The bladder was not abnormal except for a mild film of hemachrome in the base. The ureteral orifices were normal and spurted clear urine. Both sides were easily catheterized. Phenolsulphonphthalein appeared on the right side in 2½ minutes and on the left in 5. The output in 11½ minutes was 22 per cent on the right, 17 per cent on the left, with none in the bladder. Retrograde pyelograms, using 10 cc on the right and 6 cc on the left, showed a failure of rotation of the left kidney with the pelvis pointing anteromedially. No other abnormality could be seen. Acid fast stains the next day and a week later were negative. A guinea pig was also inoculated later and at autopsy showed no tuberculosis.

The patient was discharged without treatment or diagnosis, though the hematuria continued. A week later he passed some very black urine intermittently. The next day cystoscopy showed some inflammation of the urethra and of the vesical orifice. Urine from the right ureter was now grossly bloody and that from the left was clear. Urethral bleeding followed the cystoscopy and continued until the next morning, when he was admitted to the hospital because of severe chemical urethritis apparently due to the local anesthesia. The penis was enlarged and the meatus inflamed. In addition the liver edge was now tender and on deep inspiration could be felt 3 cm. below the costal margin. Hematuria continued. With Sitz baths the urethritis subsided quickly, permitting his discharge 2 days later.

While he was in the hospital several laboratory studies were done. The prothrombin time (Howell) was more than 2 hours (normal 10 minutes). Capillary fragility test (5 minutes compression with the blood pressure cuff at 100 mm.) showed 6 petechiae per square inch. The blood count was 87 per cent hemoglobin, 4,460,000 red cells, and 7200 white cells, with 64 per cent neutrophils and 36 per cent lymphocytes.

Beginning at this time Synkomen, a vitamin K preparation, 12 mg. daily, was given both orally and hypodermically in the hospital and by his local doctor after returning home. The bleeding stopped with the first dose. He soon felt well enough to return to work, though he felt that he was subject to colds for the next 6 weeks.

Urinalysis on February 13, after 2 weeks of treatment, showed 15 to 20 pus cells to the high power field, only rare red cells, and in the smear some rare cocci. On March 23 the prothrombin time (Howell) was 65 minutes, the red count was 4,200,000, and the hemoglobin 89 per cent. The excretory urogram was repeated, but showed no change from that of January 14, except reduction to normal on the diameter of the calyces. Synkomen was continued for another 2 months.

In November he had no complaints and had gained 20 pounds. He had found that he was not able to do full work during the summer on account of syncope. The urine was normal, except for a rare pus cell and 4 to 8 red cells per high power field. The blood count was 87 per cent hemoglobin and 4,470,000 red cells. Bleeding time was 1 minute and 20 seconds, coagulation time (Lee-White) was 12 minutes, prothrombin time (Quick) was 13 seconds (control 15 seconds). An intravenous urogram showed no change from the films 8 months previously.

Case 2. I. B., a 63 year old white female dishwasher, was first seen September 21, 1948. Within the last year she had two episodes of hematuria lasting one or two voidings. The present attack began a week ago as a constant chocolate brown or occasionally bright red urine, without clots. There had been left renal colic at the onset only. Treatment had been bed rest. Her past history was negative except for an occasional tarry stool for one day and mild hay fever at times. The family history revealed that her 88 year old mother had had hematuria for a year.

On examination the patient was obese, well developed, and in no acute distress. The blood pressure was 172/92. The 28 F panendoscope passed easily. Urethral varicosities were present but did not bleed easily. The left ureter was seen to spurt very bloody urine, while that from the right ureter was clear. A 10 F bulb and an 8 F catheter were passed successively 35 cm. up the left ureter without obstruction or residual urine being found. Retrograde pyelography was normal, but the films revealed a gallstone 2½ cm. in diameter. The urine was loaded with red cells but there were no bacteria, the pH was 5.5, specific gravity 1.010, a trace of albumin, and no sugar.

The patient was returned to her family doctor with instructions that she should have bleeding and clotting times, a blood count, and should be started on vitamin K therapy. A week later he reported the blood count was 3,900,000 red cells and 75 per cent hemoglobin, but that the bleeding and clotting time had not been done. On September 24 she had begun to take Synkomen, 12 mg. daily by mouth. Two days later the bleeding had almost completely stopped. On September 28 the urine showed considerable microscopic blood, the prothrombin time (Quick) was 70 seconds on one trial and 10 minutes on another, with a normal control of 42 seconds. The laboratory had just begun to do the Quick method and these variations are probably technical errors or possibly due to thrombokinase activity. Nevertheless, they show a very definite reduction in prothrombin. The clotting time (capillary tube) was 3½ minutes and the bleeding time 1 minute. Bromsulphalein liver function test gave no retention of the dye after 30 minutes.

She continued to take Synkomen for 2 weeks, though the gross bleeding had entirely stopped after 6 days' treatment. On October 9, five days after she stopped treatment, the following tests were done: Fibrinogen 136 mg. per cent (normal 200–400); platelets 220,000; total proteins 11.6; A–G ratio 1.13 to 1; clotting time (capillary tube) 3½ minutes; bleeding time 2¼ minutes; prothrombin time showed no reaction after 2 hours (control 13 seconds). The urine showed 40 to 60 red cells per high power field.

Synkomen, 2 mg. a day, was started again, and 15 days later the coagulation time (Lee-White) was 18 minutes, and the prothrombin time 15 seconds (control 13 seconds). The urine showed 4 to 6 red cells. She felt perfectly well and was instructed to continue taking vitamin K, 4 mg. daily. Four weeks later the urine contained only an occasional red cell. She was then instructed to discontinue the drug as a test of its efficacy and of her tendency to relapse. About 1 month later, on December 27, an intravenous urogram was completely normal. She felt well and was, to her sorrow, gaining weight. The urine showed 5 to 10 red cells again. The blood count was 86 per cent hemoglobin and 4,200,000 red cells. The coagulation time (Lee-White) was 4¾ minutes. Prothrombin time (Quick) was 14 seconds (control 12 seconds). She was instructed to continue Synkomen, 3 mg. every second day.

COMMENT

The cause of the hypoprothrombinemia and vitamin K deficiency in both these patients could not be determined, but the variations in liver size and tenderness in the first, and the presence of the gallstone in the second may indicate some failure in the synthesis of prothrombin due to liver disease, even though in the second patient liver function test was normal. Unfortunately no liver function studies were done in the first patient.

The great variations in the prothrombin and coagulation time readings in the second case may possibly be explained by some such deficiency as Owren's Factor V. However, the response to vitamin K administration leads one to feel that there must have been laboratory errors, and that this is actually a prothrombin deficiency.

DISCUSSION

A total of 14 cases of idiopathic hypoprothrombinemia have been found in the literature, mostly in journals not usually read regularly by urologists. In 1941 Rhoads and Fitzhugh made the first report, a 15 year old boy with a lifelong bleeding tendency. In 1938, on his seventeenth hospital admission, the former diagnosis of hemophilia without family history was corrected after finding a reduced prothrombin level of unknown cause. There were two minor attacks of hematuria among his 26 hospital admissions. Death occurred from cerebral hemorrhage at 18. Vitamin K and transfusions had only variable minor effects on the prothrombin and clotting times, which was also true in five other cases.

A patient of Beard, reported by Quick, was a white boy of 8 with the same diagnoses and a comparable history. Hematuria was not mentioned.

Heinild reports brothers, aged 4 and 1 years, with low prothrombin activity, (63 per cent and 42 per cent of normal), low fibrin levels (0.029 and 0.035 per cent), and low platelets (73,000 and 167,000 respectively). Both had bled from the stump of the cord on the seventh day after birth, and one from dilating the prepuce. The older boy was cured clinically (but not by laboratory studies) by vitamin K, but the younger boy was not benefited. A maternal aunt and uncle were said to be bleeders also, and the aunt had known hypoprothrombinemia.

Austin and Quastler's 53 year old man had a sudden onset of a bleeding tendency, including one episode of hematuria, and died within 4 months of cerebral hemorrhage. Clotting and prothrombin times were abnormal, the bleeding time was not stated. There was a variable decreasing response to vitamin K, transfusions, and other forms of treatment. Autopsy showed active pulmonary tuberculosis, retroperitoneal Hodgkin's disease, possible sarcoidosis, and granulomata, probably tuberculous, of the lungs, liver, and lymph glands. They quote Andrus and Lord, and also Rhoads, that 1 in 6 patients with hypoprothrombinemia is vitamin K fast, usually having marked liver damage.

Hauser's own report is unavailable, but Heindl, et al., state that this also was one of hereditary, vitamin K resistant, hypoprothrombinemia, with prolonged clotting time. It did not respond to transfusions. Symptoms were not mentioned.

Smith and Kaufman presented 2 women of 44 and 47 with recurrent hematuria and negative urological findings, one after repeated examination. They were found to have prothrombin times of 55 and 60 to 65 seconds, respectively, by Quick's method. Both were relieved by vitamin K, the first also cured of recurrent epistaxis. Their other patient is the only one reported in which hematuria was the only symptom of hypoprothrombinemia. They state: "Avitaminosis K occurs with moderate frequency and is sometimes the only factor of so-called essential hematuria." In spite of this statement, apparently no other such cases have been reported, even by their urological audience.

Lewis and Bennett include in their summary a woman of 29 with abrupt onset of unspecified symptoms. A prothrombin time (Quick) of 10 minutes and coagulation time of 60 minutes were found. They refer to two types of prothrombin described by Quick in 1943 and Feissly the same year as Factors A and B. This patient had almost complete disappearance of this Factor B. This is the same factor that is reduced in obstructive jaundice, cirrhosis, and dicoumarolization. In these three conditions the prothrombin time may be shortened by the administration of vitamin K, just as in the idiopathic case. The Factor A was found to be normal in all their patients with hypoprothrombinemia.

Heindl, Anderson, and Friedlander described a 43 year old white woman with sudden onset of ecchymoses even progressing to laryngeal obstruction, and also with gross hematuria. Her past history recorded only a prolonged menstrual flow beginning a month before the ecchymoses, and a gluteal tendonitis and bursitis for which she had taken 3 tablets of Empirin Compound with codiene daily for four weeks. She was cured in 12 days by massive doses of vitamin K (585.6 mg. of Hykinone) and 3 transfusions.

Owren studied a marked hemorrhagic diathesis in a 29 year old woman with repeated profuse hemorrhages in various organs, including one attack of renal colic presumably due to hematuria with clots. She was found to have a congenital, but not hereditary, absence of a previously unknown blood factor which he called Factor V, because, even though the prothrombin time was 70 to 80 seconds and the clotting time 15 minutes by the capillary tube and 25 minutes by the Lee-White method, vitamin K had no effect. A single transfusion stopped her bleeding, and he found that the Factor V isolated from only 100 cc of normal plasma would reduce her prothrombin time to 28 seconds, the effect lasting about three days.

Similar cases have been reported by Giordano, Murphy and Clark, and Quick. Giordano's patient had a marked hemorrhagic diathesis but no hematuria. That of Murphy and Clark had one admission for hematuria and otherwise resembled Giordano's. The one reported by Quick was found accidentally, never having shown a bleeding tendency. All of these 3 failed to respond to vitamin K, but were markedly helped by transfusions. All showed a distinct familial factor. Only here do they differ from Owren's case, and one may speculate that they may be manifestations of the same disorder.

Other instances of hematuria with hypoprothrombinemia may well have appeared in the nonurological literature. Moreover, physicians have undoubtedly treated, and even cured, many cases of hematuria due to idiopathic avitaminosis K without ever having a urological consultation, a prothrombin time, a clotting time, or even a diagnosis, the patient recovering after the empirical administration of vitamin K. This is suggested by the manner in which my first case was handled by the family doctor.

Evans and MacLaren reported the case of a 39 year old Greek man who complained of severe recurrent hematuria and who gave a history of lifelong bleeding involving the nose, eye, and subcutaneous tissues. Investigation revealed a strongly Mendelian dominant hereditary bleeding tendency. Here, however, the platelets were reduced, the bleeding time prolonged, while the prothrombin and coagulation times were normal. Therapy was not mentioned. The case is included here only as one of a related nature, but not the type we are discussing.

SUMMARY

Two cases of idiopathic reduction of blood prothrombin level with unilateral renal hematuria as the only hemorrhagic symptom are added to the literature. Both responded to the administration of vitamin K over long periods.

Of the 14 case reports of idiopathic hypoprothrombinemia found in the literature, 7 are stated to have had hematuria at some time. Six of the 14, one adult and five congenital types, failed to receive any consistent benefit from either vitamin K or blood transfusions. Two of these had hematuria.

In 4 patients, all adult women, vitamin K produced cure. Hematuria was a prominent symptom in 1, the presenting complaint in another, and the only symptom of prothrombin deficiency, as in our 2 cases, in a third.

In contrast to these, in 4 others the reduced prothrombin level was apparently congenital, was improved by blood transfusions, but was unaffected by vitamin K. Two of these had hematuria. The abnormality in these 4 cases may be the absence of the previously unknown blood constituent, Factor V, described by Owren.

Other obscure defects in the clotting mechanism have also been reported to cause hematuria.

CONCLUSIONS

A new cause of "essential" hematuria needs emphasis—idiopathic hypoprothrombinemia.

The recognition of this cause is important in avoiding unnecessary nephrectomy.

Any case with obscure hematuria deserves to have a blood study, including prothrombin and clotting times, as a part of the urological investigation.

Blood dyscrasias, particularly prothrombin deficiency, are probably frequently overlooked as a cause for unilateral renal hematuria.

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THE TREATMENT OF BACILLARY URINARY INFECTIONS WITH CHLOROMYCETIN[1, 2]

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It is generally supposed that normally the urinary tract from the kidneys to the urethra is sterile. However, the more one studies the bacteriologic reactions of the urine in health and disease, the more evidence there is that this hypothesis is not necessarily true.

Transient bacteriurias are common with upper respiratory infections, skin infections, vaginal, cervical, rectal and prostatic infections, but many of these become of clinical importance only when other pathologic entities of the host become evident. Most of these transient bacteriurias are subclinical and self-limiting, but on the other hand, many patients can harbor a severe chronic or latent urinary infection for years with relatively few clinical symptoms and with very little structural alteration or demonstrable impairment to physiologic function.

BACTERIOLOGY

It is the belief of many investigators that most primary urinary infections originally enter the urinary tract through the renal circulation.[3] It is thought that the usual portal of entry is presumed to be by way of the upper respiratory tract, routed through the tonsils and pharyngeal lymphoid tissue, the paranasal sinuses, devital teeth, dental caries and, less commonly, the lungs and skin. In view of the coccal bacterial flora of these regions, the urinary infections from this source are likewise primarily coccal in type.

Bacillary urinary infections on the other hand are almost entirely derived from the intestinal flora and are usually, if not exclusively, due to the migration of organisms from the colon and pelvic adnexae to the urinary tract by way of the lymphatics as well as the blood vessels.

It is our belief that bacillary infections of the urinary tract are seldom primary infections except in typhoid, paratyphoid, or kindred disease states where bacteriemias exist and the routes are probably lymphohematogenous.

Whether the kidneys act as a physiologic bacterial filter, or clinical infection

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[1] Chloromycetin (Chloramphenicol, P. D. & Co.).

[2] Read at annual meeting, American Urological Association, Los Angeles, Calif. May 17, 1949.

[3] There is still general disagreement as to the etiology and mechanism of pyogenic urinary infections.

Keyes and Ferguson (*Urology* ed. 6, 1936, chap. XVI, pp. 125–130) state "thus the exanthemata, infections of the teeth and [illegible] sinuses, etc.) that loom so large in the internists' conception of [illegible] ise of surgical nephritis. Indeed, as a general principle we think [illegible] as exciting suppurative nephritis of so gross a character that it reaches a urologist only when the bacteria reach the kidney in overwhelming doses (furunculosis, influenza) or in repeated doses (colon bacilli) or when its action is supported by some retention or local surgical lesion, the accesof the urinary tract develops, depends upon the following factors: 1) the virulence of the causative organism; 2) the persistence of the focus; 3) the immediate resistance of the host; and 4) the structural deviations of the urinary tract.

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sory cause of inflammation.—The upper urinary organs are rather immune to infection than actually sterile."

Hinman (*Principles and Practice of Urology*, 1935, pp. 528-581) discusses at length the varying types and modes of urinary infection. He states "the clinical picture of urogenital infection is dimmed by an unnecessary confusion of etiological and pathological factors. The lesions are of a complex and mixed nature, rarely have they a distinct and simple entity." He describes the routes of invasion:

A. *Urogenitogenous*
  1. Ascending invasion of the lower tract.
  2. Ascending invasion of the upper tract.
B. *Hematogenous*
  1. Primary urogenital localizations.
  2. Kidney as a bacterial filter (not normally).
  3. Bacteremia
    a. general (tbc, actinomyces, etc.) infections, fevers.
    b. focal
      skin, bone, teeth, tonsils.
      intestinal
      urogenital
C. *Lymphogenous* (has little practical significance)
D. *Acessory factors*
  1. Obstructive.
  2. Traumatic.
  3. General.

Lowsley and Kirwin (*Textbook of Urology, 1926, p. 611 et seq.*) state that infections are primarily hematogenous and "if organs are sound and invading organisms not numerous or virulent will be eliminated without effect but if organs are altered (trauma, stasis, calculus, etc.) will cause disease." Ascending infections are "uncommon, nearly impossible" and the lymphatic route they dismiss with the comment "no satisfactory proof."

They further state that "colon bacilli are the causative organisms in 85 per cent of the cases and in 74 per cent are the single infective agent. Tubercle bacilli are second with staphylococci and streptococci third; Proteus and other miscellaneous organisms are fourth."

In January 1949, at the Post Graduate Urologic Conference in Buffalo, New York, Dr. Edward N. Cook (Mayo Clinic) and Dr. Ernest Witebsky (University of Buffalo) discussed the bacteriology of urinary infections. Since formal papers were not read, Dr. George Slotkin has made available the transcriptions and the following are their direct quotations:

Dr. Witebsky states that in 9 out of 10 cases, the gram positive coccal organism is the Streptococcus faecalis or enterococcus and further believes that the most common organism cultured is E. coli with Aerobacter aerogenes a close second, Pseudomonas aeruginosa and Proteus vulgaris, third and fourth. He has little regard for the streptococci and staphylococci as pathogenic invaders and states that beta streptococcus hemolyticus has not been found more than "ten times in the past 12 to 14 years." The staphylococci in general, he considers as contaminants.

Dr. Cook states that "Helmholz has pretty definitely shown that the most common form of infection in the urinary tract is of the ascending type with the entrance through the urinary passages." He does believe the coccal infections are hematogenous but says also that "bad teeth or bad tonsils account for the rare and isolated case." He decries the "wholesale removal of teeth and tonsils." He also is in agreement with Witebsky that the gram positive cocci found are Streptococcus faecalis or enterococci and quotes Dr. Hugh Cabot as saying that "he had never seen a Proteus infection or a Streptococcus faecalis infection of the urinary tract in a patient who had not been catheterized."

Dr. Cook also states that his two most effective drugs were mandelic acid and the sulfonamides and that while he did use penicillin, he felt it was over-emphasized and the cause of a great many sensitizations. He also states: "It is very rare in my experience that I have ever had to use streptomycin for an infection in the urinary tract. That may sound rather broad. It may sound even a bit stubborn!"

It can thus be seen that there is still considerable confusion and differences of opinion both as regards to the modes of transmission of infection and to the types of organisms involved.

As a result of our observations, we believe the factors involved in bacillary urinary infections are: 1) prior acute or latent coccal infections with lowered local resistance of the urinary tract; 2) structural alterations of the urinary tract, such as anomalies, stasis, calculosis and neoplasms; and 3) accessory genital or adnexal disease.

This then could account for: 1) the relative infrequency of single strain bacterial cultures or, conversely, the great frequency of mixed bacterial flora; and 2) the frequent shifting of cultural types that occur either with or without treatment.

Studies are now under way to determine, if possible, the quantitative relationship of the bacterial flora and the mechanism of reseeding or reinvasion.

In our series of cases, about 75 per cent reveal mixed coccal and bacillary forms and, therefore, require multiple antibiotic or chemotherapeutic measures.

CLASSIFICATION OF INFECTIONS

For purpose of classification, we have divided urinary infections into three groups: 1) clinical; 2) subclinical; 3) latent.

Clinical infections may be defined as those producing both subjective symptoms and objective signs depending upon the segments of the urinary tract involved. These naturally will vary in degree and severity, depending upon the acuteness or chronicity of the infections and the associated structural pathological changes.

Subclinical infections are those in which the objective findings are prominent but the subjective symptoms are relatively minor. As an example, a patient with an asymptomatic renal calculus with pyuria and bacteriuria.

Latent infections are those where pyuria and bacteriuria are present but where structural urinary tract changes cannot be demonstrated.

CRITERIA OF "CURE"

Dr. Gilbert Thomas in a discussion of a symposium on the Use of Antibiotics in Urinary Infection at the American Medical Association Meeting in 1946, made the statement that "today investigators infrequently use the term 'cure' ".[4] We are in full agreement with this interpretation. Thus, we should like to define our results as: 1) *controlled;* symptom free, urinary cultures sterile; 2) *improved,* symptom free or clinically better, but urinary cultures positive; 3) *unimproved,* symptoms and cultures unchanged. This also includes those cases which have relapsed.

PRE-SULFONAMIDE CHEMOTHERAPY

Prior to the advent of the sulfonamides in the middle of the last decade, the chemotherapy of urinary infections was on a more or less empiric basis. Whatever benefits from the chemotherapeutic agents were probably the result of the changes in the *p*H of the urine with a varying bacteriostatic effect. It is more certain that patients got well because of surgical correction of the disease or removal of infected foci plus their own inherent immune reactions.

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[4] Thomas, G.: Discussion of symposium, The Use of Antibiotics in Urinary Infections, Section on Urology, ninety-fifth annual session of American Medical Association, San Francisco, July 4, 1946.

The appearance of the sulfonamides on the therapeutic stage, however, changed this empiric philosophy and brought about the first sound rational phase of chemotherapy and the sulfonamides still have a very definite place in our therapeutic armamentarium.

STREPTOMYCIN

The discovery and development of penicillin by English[5] and American scientists have opened wide the door to an entirely new concept of the treatment of bacterial infections. Penicillin, however, was found to have very definite limitations with regards to bacillary infections. In 1944 Waksman et al.[6] introduced streptomycin (derived from Streptomyces griseus) and this in its varying forms has proved to be rather markedly effective in bacillary as well as tuberculous infections of the urinary tract. Certain important disadvantages, however, have appeared.

1) It must be given parenterally and this is attendant with considerable patient discomfort.

2) Toxic reactions, especially cutaneous and eighth nerve involvement, are common.

3) Most important, the organisms may frequently and rapidly become highly streptomycin resistant.

CHLOROMYCETIN

Chemistry. Chloromycetin is a new crystalline antibiotic isolated from a soil actinomyces known as Streptomyces venezuelae, since it was originally discovered from specimens obtained in Venzuela by Dr. Paul R. Burkholder[7] of the Osborn Botanical Laboratory of Yale University. In 1948, it was independently isolated from culture filtrates of a streptomyces obtained from Central Illinois by Gottlieb, Bhattacharyya, Anderson and Pridham.[8]

The antibiotic is chemically different from any thus far described and has been found to contain both nitrogen and nonionic chlorine (hence its name Chloromycetin, Ehrlich, et al. 1947).[9]

Chloromycetin is a neutral compound and is very stable in acid and neutral ranges, but is unstable in strongly alkaline solutions.

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[5] Chain, E., Florey, H. W., Gardner, A. D., Heatley, N. G., Jennings, M. A., Orr-Ewing, J. and Sanders, A. G.: Penicillin as a chemotherapeutic agent. The Lancet, 2: 226–228, 1940.

Powell, H. M. and Jamieson, W. A.: Response of sulfonamide-fast pneumococci to penicillin. Proc. Soc. Exper. Biol. & Med., 49: 387–389, 1942.

Fleming, A.: In-vitro tests of penicillin potency. The Lancet, 1: 732–733, 1942.

[6] Schatz, A., Bugie, E. and Waksman, S. A.: Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. Proc. Soc. Exper. Biol. & Med., 55: 66–69, 1944.

Robinson, J. J., Smith, D. G. and Graessle, O. E.: Chemotherapeutic properties of streptomycin. Proc. Soc. Exper. Biol. and Med., 57: 226–231, 1944.

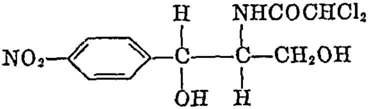
[7] Smadel, J. E. and Jackson, E. B.: Science, 106: 418, 1947.

Ehrlich, J., Gottlieb, D., Burkholder, P. R., Anderson, L. E. and Pridham, T. G.: J. Bact., 56: 467, 1948.

[8] Gottlieb, D., Bhattacharyya, P. K., Anderson, H. W. and Carter, H. E.: J. Bact., 55: 409, 1948.

[9] Ehrlich, J., Bartz, Q. R., Smith, R. M. and Joslyn, D. A.: Science, 106: 417, 1947.

Chloromycetin is[10] D(-) threo-1-p-nitrophenyl-2-diacetamido-1,3-propandiol, having the following chemical structure:



Screening tests for antibacterial activity. Extensive in vitro tests of antibiotic activity have been made (Ehrlich, et al. 1947)[9] and reveal that Chloromycetin is considerably more active against several gram negative species than against the gram positive and acid fast species tested. When compared to streptomycin, it is 2 to 16 times as active against the gram negative organisms and 7 to 36 times as active as penicillin:[11]

Susceptibility of Common Pathogens

Organism	*Source*	*Inoculum*	*Inhibiting Concentration γ/ml.*
Aerobacter aerogenes	Stock	1–20,000,000	0.5
Alcaligenes fecalis	Pus	1–10,000,000	1.0
Bacillus anthracis	B.A.I.	1–20	5.0
Diplococcus pneu. I	Pus	1–10,000,000	1.0
Diplococcus pneu. III	Stock	1–10,000,000	2.5
Escherichiae coli	Urine	1–20,000,000	2.5
Escherichiae coli	Blood	1–10,000,000	2.5
Klebsiella pneu	Sputum	1–10,000,000	0.75
Klebsiella pneu. I	Urine	1–10,000,000	2.5
Klebsiella pneu. II	Urine	1–5,000,000	15.0
M. pyogenes albus	Vagina	1–10,000,000	2.5
Pseud. aeruginosa	Urine	1–10,000,000	10.0
Salmonella enterit	Stock	1–10,000,000	0.75
Salmonella paratyphi	Stock	1–10,000,000	2.5
Salmonella typhosa	Stool	1–10,000,000	1.0
Streptococcus hemol	Abscess	1–5,000,000	2.5
Streptococcus lactis	Milk	1–5,000,000	0.75
Streptococcus nonhemol	Stock	1–10,000,000	0.75

Organisms	*Penicillin, μg/ml.*	*Chloromycetin μg/ml.*	*Ratio, P/C*
E. coli	8.4	0.33	25
K. pneumonia	2.4	0.33	7
S. schottmuller	2.4	0.33	7
S. paradysenteriae (Sonne)	7.2	0.20	36
S. aureus	0.018	1.0	0.018

	Streptomycin, μg/ml.	*Chloromycetin, μg/ml.*	*Ratio, S/C*
E. typhus	1.66	0.36	4.61
E. coli	2.50	0.50	5.00
K. pneumonia	0.55	0.25	2.20
P. vulgaris	8.00	0.50	16.00
S. schottmuller	1.66	0.50	3.32
S. paradysenteriae (Sonne)	1.00	0.33	3.00
S. aureus	1.66	1.0	1.66

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[10] Rebstock, M. C., Crooks, H. M., Controulis, J. and Bartz, Q.: Jour. Am. Chem. Soc. In press.

[11] Smith, R. M., Joslyn, D. A., Gruhzit, O. M., McLean, Jr., I. W., Penner, M. A. and Ehrlich, J.: J. Bact., 55: 425, 1948.

Experiments have shown that Chloromycetin possesses little or no antifungal, antiprotozoal* and antimalarial activity, but has shown remarkable antirickettsial activity and clinical experiments, reported elsewhere in both epidemic and scrub typhus have been little less than sensational and that all treated patients promptly recovered.[12]

Pharmacology of Chloromycetin in animals. Extensive pharmacologic studies in small animals and dogs show that Chloromycetin administered in fairly large doses (85–80 mg/kg/day) intramuscularly for 24 days and 0.5 gm. twice daily orally revealed no significant changes in total white cell or differential counts, blood nonprotein nitrogen, blood sugar; nor were alterations of behavior referable to drug toxicity noted. The urine of all animals remained consistently free of albumin and reducing sugar. The urinary *p*H and specific gravity were within normal limits.

The oral ingestion of Chloromycetin showed serum and urine concentrations greatest from the fourth to eighth hour. There was no evidence of slow accumulation of the drug in the body.[11]

Absorption and excretion of Chloromycetin in man. The concentration levels of Chloromycetin in the serum and urine of the cases described here were checked at frequent intervals during the course of therapy. A microbiological assay procedure[12] was used to determine the concentration of active antibiotic, and a colorimetric method[13] was used to determine the concentration of total drug including inactive degradation products of Chloromycetin.

Chloromycetin was found to appear in the blood shortly after oral administration, indicating rapid absorption from the gastro-intestinal tract. Data presented in table 1 show the serum concentration of Chloromycetin in a human subject following administration of a single 3 gm. dose by mouth, in the form of 0.25 gm. tablets. The maximum concentration in serum was found in about 2 hours, and the level fell off gradually thereafter, with a return to normal after 22 hours. In a few cases absorption was delayed, with peak serum levels being reached in 6 to 8 hours. Results illustrating this condition are presented in table 2. The slow absorption has not been adequately explained, and may be due to tablets having poor disintegration qualities, or perhaps to some influence of high concentrations of Chloromycetin on absorption processes. However, the majority of cases showed fairly rapid absorption, with maximum serum levels being reached within 4 hours of the time of administration.

The urinary excretion of Chloromycetin was studied in the same patient whose

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Payne, E. H., Knaudt, J. A. and Palacios, S.: Treatment of epidemic typhus with chloromycetin. J. of Trop. Med. and Hyg., 51: 68–71, 1948.

Smadel, J. E., Woodward, T. E., Ley, Jr., H. L., Philip, C. B., Taub, R., Lewthwaite, R. and Savoor, S. R.: Science, 108: 160, 1948.

Woodward, T. E., Smadel, J. E., Ley, Jr., H. L., Green, R. and Mankirar, D. S.: Ann. Int. Med., 29: 131, 1948.

Payne, E. H., Sharp, E. A. and Knaudt, J. A.: Tr. Roy. Soc. Trop. Med. & Hyg., 42: 163, 1948.

Smadel, J. E., Leon, A. P., Ley, H. L. and Varela, C.: Proc. Soc. Exp. Biol. & Med., 68: 12, 1948.

* Chloromyceitin has been found effective in acute syphilis since this was written.

[12] Glazko, A. J., Wolfe, L. M. and Dill, W. A.: To be published.

[13] Joslyn, D. A. and Galbraith, M.: To be published.

blood levels are presented in table 1. Complete collections of urine were made at stated intervals and the urine volumes were measured for each collection period. Samples were then analyzed by the chemical and microbiological assay procedures. The results are given in table 3.

It is evident that the excretion rate closely parallels the Chloromycetin concentration in the serum (table 1). In addition, a wide discrepancy is noted between the chemical and microbiological assay figures for urine, whereas the values for serum concentrations are fairly close. This is attributed to the presence of inactive metabolic products of Chloromycetin in the urine. The principal excretory product has been isolated and identified as a conjugate of Chloromycetin with glucuronic acid.[14] About 80 per cent of the administered dose is accounted for by

TABLE 1. *Concentration of chloromycetin in serum*

A normal human subject was given 3.0 gm. of Chloromycetin by mouth, and blood samples were drawn at stated intervals for assay by the chemical and microbiological procedures.

TIME AFTER ADMINISTRATION	CONCENTRATION OF CHLOROMYCETIN IN SERUM	
	Microbiological assay	Chemical assay*
hr.	*micrograms per ml.*	*micrograms per ml.*
2	49	51
4	35	42
6	30	36
8	17	25
10	12	20
14	8	11
22	1	3

* The chemical assay includes inactive degradation products of chloromycetin.

TABLE 2. *Concentration of Chloromycetin in serum*

Patient (G. L. McK., fig. 1) was given 3.0 gm. of Chloromycetin by mouth and blood samples were drawn at frequent intervals thereafter for assay by the chemical and microbiological procedures.

TIME AFTER ADMINISTRATION	CONCENTRATION OF CHLOROMYCETIN IN SERUM	
	Microbiological assay	Chemical assay*
hr.	*micrograms per ml.*	*micrograms per ml.*
0.5	15	17
1.0	11	13
1.5	11	13
2.0	9	15
2.5	9	16
3.5	10	24
6.0	31	43
28.	2.5	6

* Chemical assay includes inactive degradation products of Chloromycetin (see case 1).

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[14] Glazko, A. J., Wolf, L. M., Dill, W. A. and Bratton, Jr., A. C.: Tissue distribution and excretion of chloramphenical (chloromycetin). To be published J. Pharmacol. and Exper. Therap.

urinary excretion in 24 hours, but only 15 per cent of the dose is excreted as active Chloromycetin. The actual concentration of Chloromycetin in urine varies with urine volume, but in most patients a level of over a hundred micrograms of active antibiotic per ml. of urine is maintained for periods well over 8 hours following a single 3 gm. dose (table 3). This, of course, is far greater than necessary to inhibit the growth of susceptible gram negative bacteria.

Dosage. The ultimate objective of an antibiotic is the control of disease. Since the in vitro tests of the antibacterial activity of Chloromycetin revealed such a high order of effectiveness in the gram negative bacilli, the next step was to determine the therapeutic effectiveness in urinary infections of this nature. Likewise since it was demonstrated that Chloromycetin could be administered orally all studies were carried out in this manner. At first the antibiotic was given in tablet form but there appeared to be some difference in absorption rates (possibly due to different degree of tablet compression) and some patients complained of certain adverse taste reactions due to a peculiar pungency and odor. Later sealed capsules were substituted and no further difficulty was encountered.

TABLE 3. *Urinary excretion of Chloromycetin and its metabolic products*

Blood levels for this patient are given in table 1. Patient received a 3 gm. oral dose of Chloromycetin, and urine samples were collected at stated intervals. Samples were analyzed by the chemical and microbiological assay technics.

TIME AFTER ADMINISTRATION	URINE VOLUME	MICROBIOLOGICAL ASSAY			CHEMICAL ASSAY*		
		Concentration	Amount excreted	Excretion rate	Concentration	Amount excreted	Excretion rate
hr.	*ml.*	*μg/ml.*	*mg.*	*mg./min.*	*μg/ml.*	*mg.*	*mg./min.*
0	340	0	0	0	0	0	0
2	500	125	63	0.52	320	160	1.33
4	800	160	128	1.07	500	400	3.33
6	720	140	101	0.83	550	396	3.30
8	150	210	32	0.26	1630	245	2.04
18	765	140	107	0.18	1120	855	1.43
24.5	715	34	24	0.06	500	357	0.92
Total drug excreted (mg.)			455			2413	
Per cent of dose recovered			15.2			80.4	

* Chemical assay values include inactive degradation products of Chloromycetin.

A variety of dosage patterns were studied ranging from large single doses (3.0 gm.) to smaller doses (1.0 to 1.5 gm.) in divided amounts from 0.25 to 0.5 gm. at 6 to 8 hour intervals around the clock. In general it can be said that the latter (1.0 to 1.5 gm. for 24 hours) is the optimum dosage with possibly in severe cases an initial dose of 1.0 gm. to establish an early high serum level.

Selection of Cases. No particular selection of cases was made except that bacillary urinary infection was of major importance. Wherever possible complete urologic surveys including cystoscopy, excretory and retrograde urograms, appropriate blood studies, frequent urinalysis and urine cultures as well as accessory studies were done.

Approximately 70 per cent of the patients had been unsuccessfully treated with chemotherapy and other antibiotics prior to the administration of therapy. In addition, it was early recognized that since such a high percentage of mixed infections was encountered (65 per cent), adjunct therapy was necessary. As a result, penicillin and sulfonamides were administered whenever mixed infections were found. Likewise every effort was made to carry out surgical measures and eradicate or correct focal sources if such circumstances existed.

Fifty cases have been observed and treated and comprise this report (table 4). Many others are still under observation but it is believed that these data are too recent to be of adequate value. Of these 50 patients, 38 had major structural urinary tract pathological changes such as calculi, prostatic hypertrophy, carcinoma or other disease states. Almost without exception these patients were clinically benefited but unless improvement was sustained they were listed as unimproved or relapsed. In fact, each of the 9 cases listed as unimproved had severe complicating pathological changes from which no permanent improvement was considered possible.

Reactions. Except for distaste and adverse patient comments on the antibiotic in tablet form, there were no toxic or allergic manifestations associated with the administration of Chloromycetin except in 1 case (No. 6), a nervous apprehensive man of 60 who developed a severe urinary infection in a neurogenic bladder which followed an abdominoperineal resection of the lower bowel for carcinoma of the sigmoid and rectum. He complained of a transient mild vertigo after having been questioned in this regard. These symptoms lasted almost 5 days and disappeared spontaneously.

No skin sensitivities such as dermatitis or urticaria were noted. Likewise no nausea, vomiting or diarrhea developed. In fact, there was a singular absence of any symptoms which could have been attributed to the drug.

One patient, a doctor (No. 13) received a total of 53.5 gm. over a period of 6 consecutive weeks with no reactions of any sort.

However, in spite of all this one should be warned that reactions and sensitivities will probably occur and they should always be considered a possibility and watched for. Furthermore, while Chloromycetin has been administered to patients with low renal function and elevated serum nonprotein nitrogen the increased possibilities of toxic manifestations and dangerously high serum levels should be guarded against.

Observations. Simple bacillary urinary infections, uncomplicated by major urologic pathological changes usually present few problems. The therapeutic response is rapid and often dramatic. The temperature, if elevated, usually becomes normal within a few hours and a grossly purulent urine becomes clear and free of leukocytes and bacilli within 24 to 36 hours. Urinary cultures likewise quickly become sterile. Dosage, however, should be adequate and patients should be followed for a sufficient period of time to determine permanent results.

Complicated urinary infections where coccal organisms are present require proper adjunct therapy either with penicillin or the sulfonamides (tables 4, 5 and 6). It will be noted that penicillin dosages also should be adequate. Elimina-

TABLE 4. *Summary of cases*

B, bacilli; C, cocci; U, unimproved; I, improved; C, controlled

CASE	SEX AND AGE	DIAGNOSIS	ORGANISMS	PREVIOUS TREATMENT	CHLOROMYCETIN	ADJUNCT THERAPY	RESULTS					CODE
							Symptoms	Cultures		Stain		
								B	C	B	C	
G. L. McK. (fig. 1)	M 57	Chronic cystitis with urethral stricture and multiple diverticula	Ps. aeruginosa; Nonhemolytic streptococcus viridans	Transurethral prostatic resection; penicillin; streptomycin; sulfonamides	June, '48: 1st dose 3.0 gm.; 1.0 gm. bid. Total 7.0 gm. Dec. '48: 2nd course 0.5 Gm. tid. Total 10.5 Gm.	Penicillin in *oil 0,000,000* u	Improved *(relapsed)*	+++	++	+++	++	U
B. W. (fig. 2)	F 42	*Hemorrhagic cystitis* recurrent	E. *coli*, hemolytic; Hem. strep.; Ae. aerogenes; Gr. + diplococci, unident.	Sulfonamides, penicillin in oil; streptomycin (reaction)	First dose 1.0 gm., p.5 gm. tid. Total: 5.0 gm.	None	Improved	−	+	−	+	I
J. B. D.	M 52	Recurrent bil. epididymitis; chr. cystitis	E. coli; hemolytic strep.	Penicillin in oil; sulfonamides	1.0 gm. 4 x daily (Sept. '48). Total 0.0 gm. (Jan. '49); 0.5 gm. tid. Total 10.0 gm.	None	Improved	+	+	+	+	I
O. K.	F 52	Post-op. neurogenic bladder; carcinoma of rectum	E. coli; Ae. aerogenes; non-hem. strep.	Penicillin; streptomycin sulfonamides; pyridium	1.0 gm. tid. Total 7.0 gm. (July '48). 0.5 gm. tid. Total 7.0 *gm.* (Aug. '48)	None	Unimproved (relapsed)	++++	+++	++++	++	U
T. B.	M 55	Chr. pyelonephritis, bil.; atrophic right kidney	Ae. aerogenes; cocci, unidentified	Penicillin; sulfadizine, (reaction)	1.0 gm. qid.—Total 4.0 gm. June '48. 0.5 gm. qid.—Total 4.0 gm. July '48	None	Improved	+	−	+	+	I
E. B.	M 60	Post-*op.* neurogenic *bladder; ca. of* sigmoid colon	*Ps.* aeruginosa	Penicillin; sulfonamides; streptomycin	3.0 *gm. 1st dose, then* 0.5 gm. tid. Total 9.0 gm.	*None*	*Improved* (vertigo 5 days)	−	−	−	−	C

J M	M 64	Acute pyelonephritis, diabetes mellitus, uterine fibroid	Salmonella A , Ae aerogenes, Ps aeruginosa, Gr positive diplococcus, unident	Penicillin	3 0 gm 1st dose, then 0 5 tid Total 12 0 gm	Penicillin	Improved	—	—	—	—	C
G H (fig 3)	F 36	Recurrent cystitis, acute	Ae aerogenes, unident strep	Penicillin, sulfonamides	2 0 gm 1st dose, then 0 5 gm tid Total 4 5 gm	None	Improved	—	—	—	—	C
T Z (fig 4)	F 30	Chr pyelonephritis, right hydronephrosis	E coli	Sulfonamides	1 0 gm 1st dose Total 6 0 gm	None	Improved	—	—	—	—	C
T L	M 37	Chr urinary infection	Ps aeruginosa, strep unident	None	1 0 gm 1st dose Total 6 0 gm	Penicillin 9,000 000 u	Improved	—	—	—	—	C
H B (fig 5)	M 63	Chr urinary infection, renal calculus, right	Ps aeruginosa, Gr positive cocci unident , Klebsiella, Ae aerogenes	Penicillin, streptomycin (2 unsuccessful operations for removal of calculus by osteopaths)	1 0 gm 1st dose Total 6 0 gm (Sept '48) 0 5 gm tid Total 6 0 gm (Dec '48)	None	Improved (relapsed)	++	—	++	—	U
J S	M 78	Calculus filled diverticula of bladder, mult calculi lt kidney, massive urinary infection	Proteus, gram positive cocci, unident	Sulfonamides, mandelic acid, penicillin	0 5 gm tid Total 8 0 gm	None	Improved (relapsed)	+++	—	++	—	U
C S	M 40	Chr urinary infection, chr prostatitis	Ae aerogenes E coli, Ps aeruginosa, non hem staph albus	Penicillin, streptomycin, sulfonamides, mandelic acid, methenamine	0 5 gm qid Total 26 0 gm 0 25 Gm qid Total 17 0 gm 0 25 gm plus sulfadiazine Total 10 5 gm Total therapy 53 5 gm	Sulfadiazine	Improved	+	—	—	—	I
M I	F 55	Chr urinary infection, atrophic left kidney, unknown path rt kidney	E coli	None	0 5 gm tid Total 6 0 gm	None	Improved	—	—	—	—	C

TABLE 4.—*Continued*

CASE	SEX AND AGE	DIAGNOSIS	ORGANISMS	PREVIOUS TREATMENT	CHLOROMYCETIN	ADJUNCT THERAPY	RESULTS					CODE
							Symptoms	Cultures		Stain		
								B	C	B	C	
F. L. Mc.	F 55	Recurrent urinary infection	Ae. aerogenes; unident. Gram. positive cocci	Penicillin; streptomycin; sulfonamides; Mand. acid	1.0 gm. 1st dose. Total 5.0 gm.	None	Improved	—	—	—	—	C
W. B. S.	M 67	Chr. urinary infection; ca. of bladder & prostate	Ae aerogenes; Proteus; Klebsiella	Penicillin; transurethral resection of prostate	3.0 gm. single dose followed by 0.5 gm. tid. Total 12.0 gm.	Penicillin	Unimproved (died)	+++	+	+++	++	U
D. C.	M 57	*Acute urinary infection*	E. coli; hemolytic streptococci	None	1.5 gm. 1st dose. Total 7.0 gm. (Sept. '48). *0.5 gm. tid. Total* 6.0 gm. (Nov. '48).	Penicillin 14,000,000 u	Improved	—	—	—	—	C
S. L.	M 52	Hypertrophy of prostate, benign	E. coli; Staph. albus	Penicillin 6,000,000 u; Streptomycin 7.0 gm. Suprapubic prostatectomy.	0.5 gm. tid. Total 10.5 gm. (Dec. '48) 0.5 gm. *tid. Total* 4.5 gm. (Jan. '49).	None	Improved	+	—	—	—	I
M. B.	M 66	Acute urinary infection C.V.R. disease	Klebsiella	None	0.5 gm. tid. Total 5.25 gm.	None	Improved	—	+	—	—	I
P. H.	F 28	Acute *cystitis*; chr. endocervicitis	E. coli; non-hem. *strep*; non-hem. staph.	Penicillin 3,000,000 u	0.5 gm. tid. Total 9.0 gm.	Penicillin 3,000,000 u Sulfonamides	Improved	—	+	—	—	I
J. H. T.	F 82	Chr. cystitis acute flareup; ca. of bladder, post-operative	Proteus; Ae. aerogenes; E. coli.	Penicillin; streptomycin; mandelic acid; sulfonamides.	0.5 gm. tid. Total 9.0 gm.	None	Improved	+	—	+	—	I
D. W.	F 44	Acute pyelonephritis; cirrhosis of liver	E. coli. Non-hem. strep.	Penicillin & streptomycin (discontinued because of skin reaction.)	1.0 gm. tid. Total 12.0 gm.	Penicillin 6,000,000 u. (c Bendryl)	Improved	—	—	—	—	I

A. R.	M 39	Acute pyelonephritis	E. coli	Sulfonamides.	0.5 gm. tid. Total 10.5 gm.	None	Improved	–	–	–	–	C
E. L.	F 47	Acute cystitis	E. coli; non-hemolytic strep.	None	0.5 gm. tid. Total 4.5 gm.	None	Improved	–	+	–	–	I
S. W.	M 83	Acute cystitis; prostatic hypertrophy, benign; diverticulum of bladder	E. coli.	Sulfonamides; suprapubic prostatectomy	2.0 gm. 1st dose. Total 5 gm. (Dec. '48) 0.5 gm. tid. Total 6.0 gm. (Jan. '49) 0.5 gm. tid. Total 6.0 gm. (Feb. '49).	Penicillin in oil	Improved	+	–	+	–	I
A. L.	M 61	Chr. cystitis; carcinoma of prostate	Ae. aerogenes; hemolytic strep.	Penicillin; sulfonamides	0.5 gm. tid. Total 6.0 gm.	None	Improved (temporary)	+	+	+	+	U
B. B.	F 86	Temporary paralysis of bladder following fracture of femur	Ps. aeruginosa	Sulfonamides Streptomycin } reaction	0.5 gm. bid. Total 2.0 gm.	Indwelling catheter	Improved	+	–	+	–	I
R. L.	M 65	Chr. cystitis; recurrent blood dyscrasia	Ps. aeruginosa (highly resistant)	Penicillin; sulfonamides	0.5 gm. tid. Total 18.0 gm.	Penicillin 10,000,000 u	Unimproved	+++	–	+++	–	U
F. Mc.	F 33	Chr. cystitis; chr. pelvic cellulitis	E. coli; Ae. aerogenes; hem. & non-hem. Staph. aureus	None	0.5 gm. tid. Total 9.0 gm.	Penicillin in oil 6,000,000 u	Improved	–	+	–	–	I
W. A. P.	M 79	Chr. urinary infection; horseshoe kidney	Ps. aeruginosa; E. coli; hemolytic strep.	Penicillin; streptomycin	0.5 gm. tid. Total 6.0 gm.	Penicillin in oil 3,000,000 u	Improved	+	+	–	+	I
A. S.	F 31	Chr. urinary infection; fractured pelvis	Klebsiella; unident. strep.	None	3.0 gm. 1st dose Total 12.0 gm.	Penicillin in oil	Improved	+	–	–	–	I
R. L. W.	F 63	Rt. ureterocutaneous anastomosis with hydronephrosis; left nephrectomy	Proteus; hem. & non-hem. staph.	Penicillin	0.5 gm. tid. Total 6.0 gm.	Penicillin in oil 6,000,000 u	Improved (temporary)	+	+	+	+	I
H. F. S.	M 60	Carcinoma of prostate	E. coli; Bact. faecalis alk.	Penicillin (suprapubic prostatectomy)	0.5 gm. tid. Total 10.0 gm.	Penicillin in oil 3,000,000 u	Improved	+	–	+	–	I

TABLE 4.—*Concluded*

CASE	SEX AND AGE	DIAGNOSIS	ORGANISMS	PREVIOUS TREATMENT	CHLOROMYCETIN	ADJUNCT THERAPY	RESULTS					CODE
							Symptoms	Cultures		Stain		
								B	C	B	C	
V. O. D.	F 58	Pyonephrosis, left; renal calculus, left	Ae aerogenes; non-hem. strep.; non-hem. corynebact.	Penicillin (left nephrectomy)	0.5 gm. tid. Total 9.0 gm.	Penicillin in oil 6,000,000 u	Improved	—	—	—	—	C
A. H.	F 23	Chronic urinary infection; ectopic left kidney	E. coli	Unknown	0.5 gm. tid. Total 12.0 gm.	Penicillin in oil 1,800,000 u	Improved	—	—	—	—	C
E W.	M 58	Acute hemorrhagic cystitis	Orig. culture lost; gr. neg. & gr. plus cocci. on stain	None	0.5 gm. tid. Total 12.0 gm.	Penicillin in oil	Improved	—	—	—	—	C
P. K.	M 49	Chr. left pyelonephritis; renal calculus, left	E. coli. Aer. aerogenes; hem. strep.	None (pyelolithotomy, left)	3.0 gm. 1st dose. Total 9.0 gm.	Penicillin in oil 4,500,000 u	Improved	—	—	—	—	C
D. J.	M 49	Acute urethritis	No organisms cultured or found on repeated stain; considered virus	Sulfonamides; penicillin in oil 4,800,000 u; neoarsphenamine	2.0 gm. 1st dose. Total 15.0 gm.	(Now improved with dilute $AgNO_3$ irrigations and mapharsen)	Unimproved	0	0	0	0	U
S. K.	M 25	Acute urethritis	Same as above	Sulfonamides (reaction); Penicillin 10,000,000 u; mapharsen; ant. irrigations dilute $AgNO_3$	2.0 gm. 1st dose. Total 12.0 gm.		Improved	0	0	0	0	I
J. L. R.	F 52	Chr. cystitis; chr. urethritis; double kidney, rt.; acute pyelonephritis	Gr. neg. bacilli on stain (not found in culture); non-hemolytic strept.	Sulfonamides; penicillin; mandelic acid	2.0 gm. 1st dose. Total 4.5 gm.	None (Therapy inadequate)	Improved (temporary, relapsed)	+	+	—	+	U

1949- Vol-62 July No1

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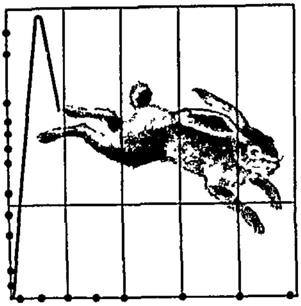

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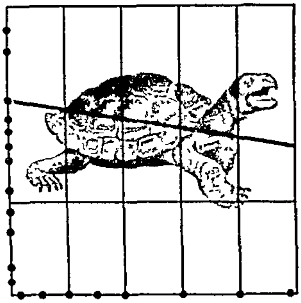

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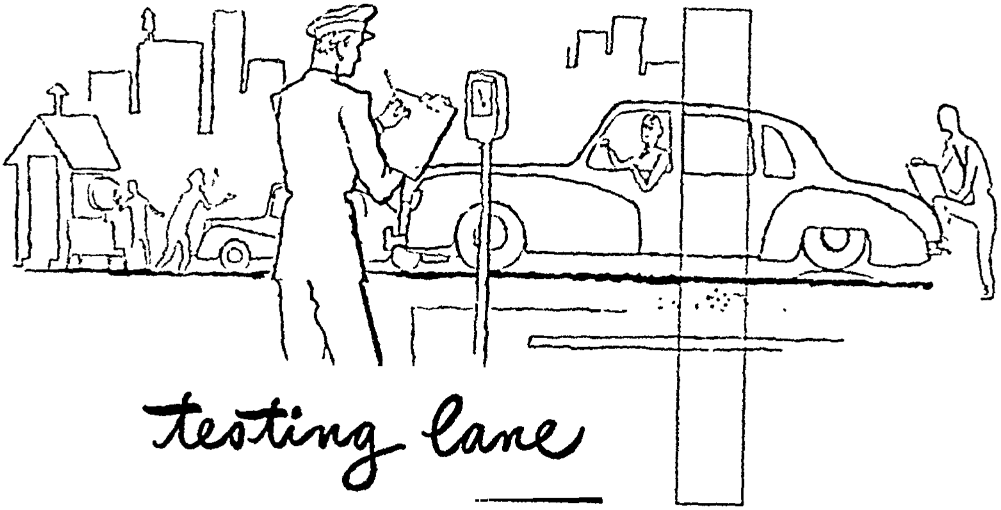

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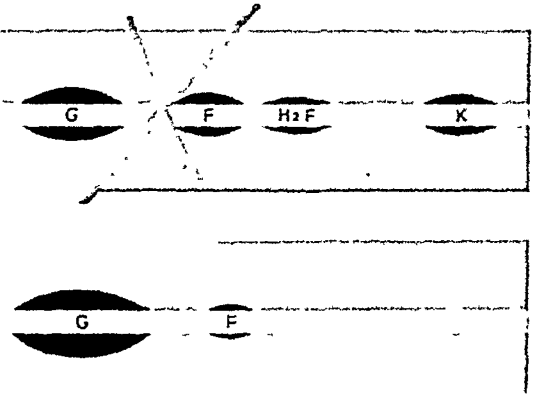

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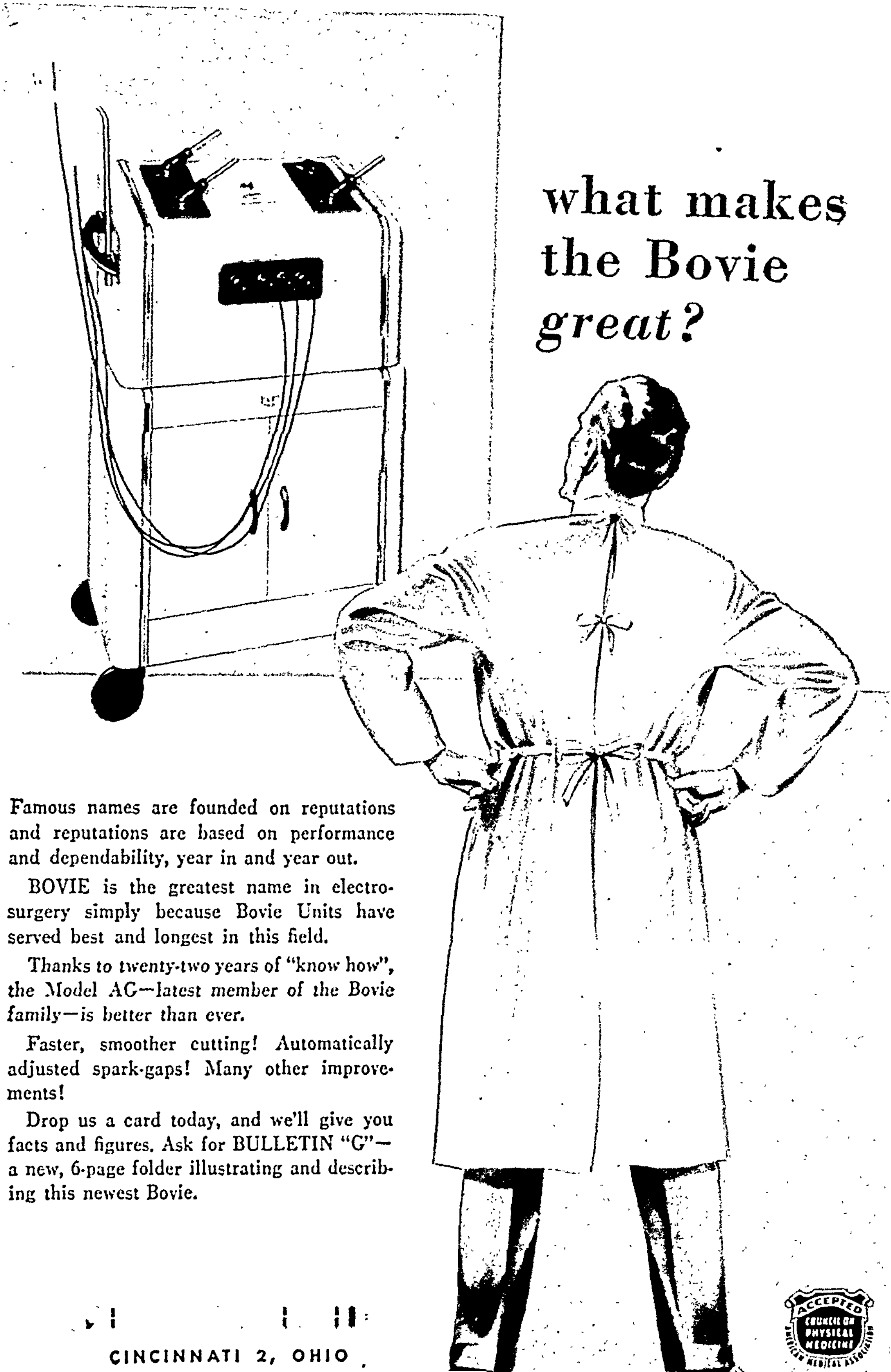

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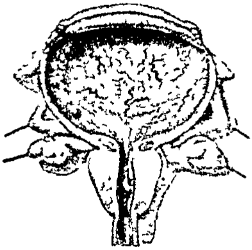

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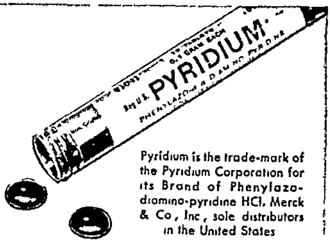

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1. Carroll, G., and Allen, N. H.: J. Urol. 55: 674 (1946).

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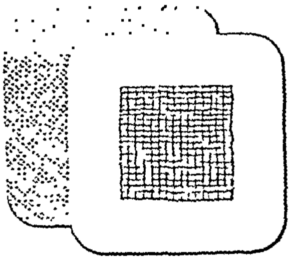

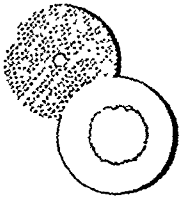

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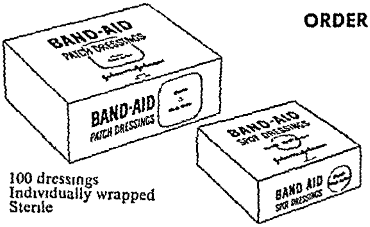

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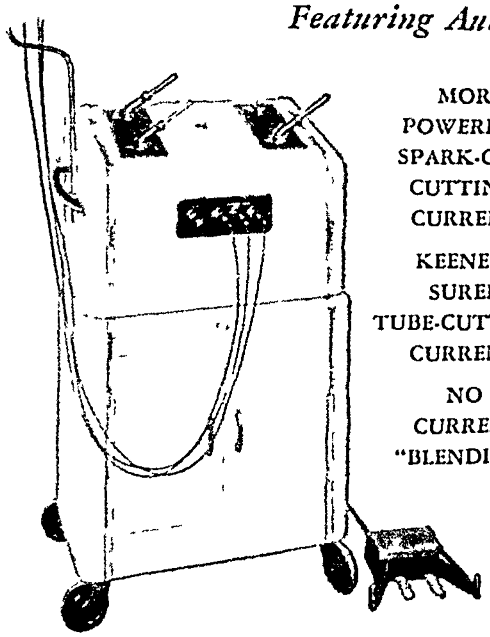

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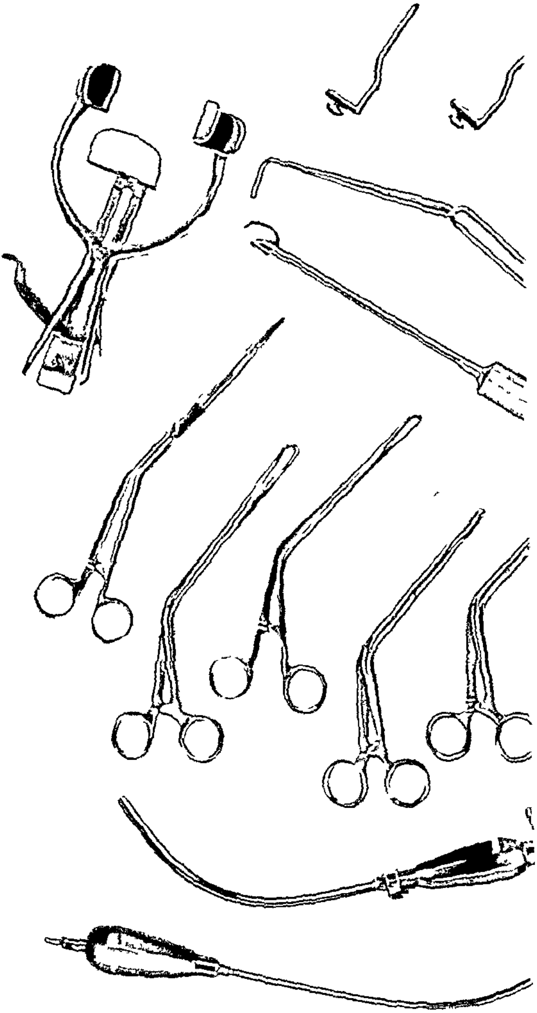
*Millin, Terrence: J Urol., 59 267, March 1948



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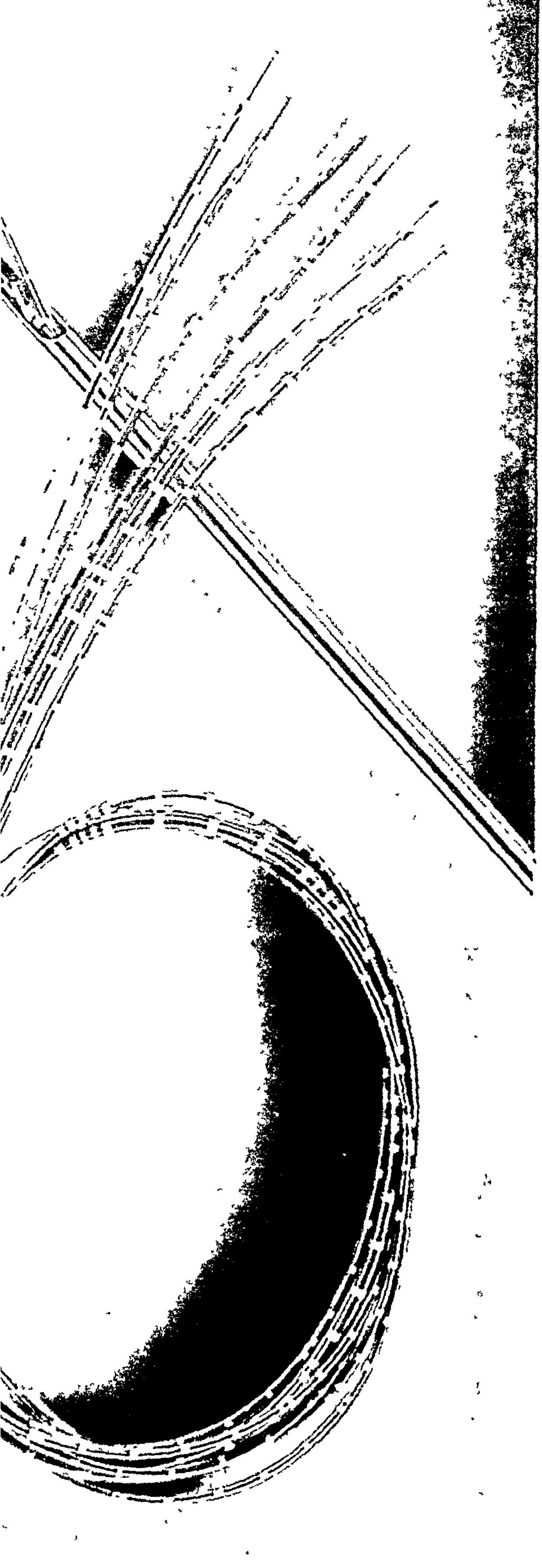

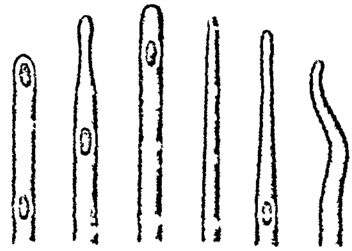

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EXPERIENCES WITH FIBRIN COAGULUM IN PYELOLITHOTOMY[1]

J HARTWELL HARRISON AND B E TRICHEL

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The removal of multiple calculi from the renal pelvis and its calyces for years has tried the ingenuity of the surgeon Inadequate methods have resulted in undue trauma to the renal parenchyma, incomplete removal of calculi, recurrent nephrolithiasis, and at times even unnecessary nephrectomy The use of the roentgenogram of the surgically exposed kidney was a great step forward in the accurate localization of calculi to facilitate their removal and also to demonstrate the incomplete removal of radio opaque calculi[2, 3, 4] It is not a rare experience to find at operation more calculi in the renal pelvis than previously had been anticipated This is due to the interposition and superimposing of large and small calculi as well as to their varying degrees of radio opacity The technique of overdistending the renal pelvis with saline solution with the ureter occluded and quickly withdrawing the pyelotomy or ureterotomy tube has served well in washing out elusive calculi and sand from the pelvis but this method leaves much to be desired A significant contribution to the surgery of renal calculus lies in the original work of Dees[5, 6, 7, 8] in the application of fibrin coagulum to pyelolithotomy The method has not been more widely employed because of the unavailability of fraction I of human blood plasma It is hoped that very soon materials for coagulum pyelolithotomy will be available for general distribution through commercial channels[9] In a recent panel discussion on renal lithiasis at a large surgical meeting in this country only a brief mention of the method was made in passing which indicated that its merits are too little appreciated at the present time by even the most experienced surgeons It is the purpose of this communication to illustrate a technique which essentially conforms to that described by Dees and to emphasize the value of the method in selected cases

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[1] The products of plasma fractionation employed in these operations were produced by the Department of Physical Chemistry in collaboration with Lederle Laboratories, Inc from blood collected by American Red Cross under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University

[2] Sosman, M C Renal roentgenography during operation Surg, Gynec & Obst, **41** 682, 1925

[3] Quinby, W C A note on the localization of renal calculi by aid of x ray films made during operation Trans Am Assoc of Genito Urin Surg, **17** 199–200, 1934

[4] Oppenheimer G D Evaluation of roentgenography of surgically exposed kidney in treatment of renal calculi J Urol, **43** 253, 1940

[5] Dees, J E and Fox H The properties of human fibrinogen coagulum Preliminary report J Urol, **36** 167, 1943

[6] Dees J E Use of an intrapelvic coagulum in pyelolithotomy Preliminary report South Med J, **49** 503, 1943

[7] Dees, J E Fibrinogen coagulum as an aid in operative removal of renal calculi J Clin Invest, **23** 576, 1944

[8] Dees, J E The use of fibrinogen coagulum in pyelolithotomy J Urol, **56** 271–283 1946

[9] Cutter Laboratories, Berkeley, Calif

Coagulum pyelolithotomy has been used for removal of a single calculus in the infundibulum of a calyx, calyceal calculi, single calculi associated with calcific debris in the renal pelvis, multiple calculi in the pelvis and calyces and for clearing the pelvis after complete obstruction by a single stone at the ureteropelvic junction. The method is particularly indicated when several small stones are demonstrable in the renal pelvis by roentgenogram (case 1) and when multiple calculi are suspected though not definitely shown before operation (case 2). The removal of single inaccessible and multiple calculi has been greatly facilitated by the technique. Fragmentation of calculi during removal has been avoided. Trauma to the kidney has been reduced to a minimum and complete mobilization of the kidney was found to be unnecessary where this procedure was undesirable. Mobilization of the kidney was carried out when the extrarenal portion of the pelvis was small. Those calculi which are densely adherent to the mucosa of the pelvis, those which are trapped in calyces having constricted infundibula, the calcified renal papilla and the large branching calculus will naturally not be extruded in the coagulum and must be removed by extraction. However, even in such cases the coagulum may be helpful in removing other free calcareous components. It should be emphasized that fibrinogen and thrombin should not be used after the kidney has been traumatized by surgical removal of calculi which has resulted in bleeding into the pelvis lest intravascular injection occur. However, the coagulum may be formed in the pelvis prior to the removal of these fixed stones.

The fraction I of human blood plasma and thrombin which we have used was prepared and made available by the Department of Physical Chemistry, Harvard Medical School. According to the technique and instructions issued, a single unit of Fraction I of human blood plasma is dissolved in 100 cc of a buffer solution of sterile 0.15 M Na_2HPO_4 thirty minutes before use. Physiological saline solution is now dispensed with the commercial preparation of fibrinogen as the diluent to dissolve the fibrinogen. When this is injected with thrombin or clotting globulin (Lederle)[5] coagulation of fibrinogen occurs within 30 seconds and it has been shown that within 4 minutes[5] that the tensile strength of this coagulum is 10 to 20 times as great as that of human blood clot. The production of this intrapelvic coagulum has no detectable effect on the kidney. In fact it is expected by us that bovine fibrinogen may be safely and satisfactorily used instead of human fibrinogen.

The steps in operative technique outlined by Dees[5] have been followed with success and are outlined below, as well as illustrated in the accompanying drawings.

1) Figure 1, *1* shows the kidney mobilized for demonstration purposes with the ureter and renal pelvis exposed. Stay sutures have been placed on either side of the ureteropelvic junction in preparation for a vertical incision in the ureter 4–5 mm. in length. One of the advantages of the technique is that removal of multiple calculi from the pelvis may be accomplished without mobilization of the kidney. When the pelvis is chiefly intrarenal in type mobilization of the kidney is desirable and better exposure can be obtained by retraction of the parenchyma overlying the renal hilus.

2) Figures 1, *2* and 2 show insertion of a soft rubber urethral catheter 12 to 14 F through the opening in the ureter into the renal pelvis The ureter

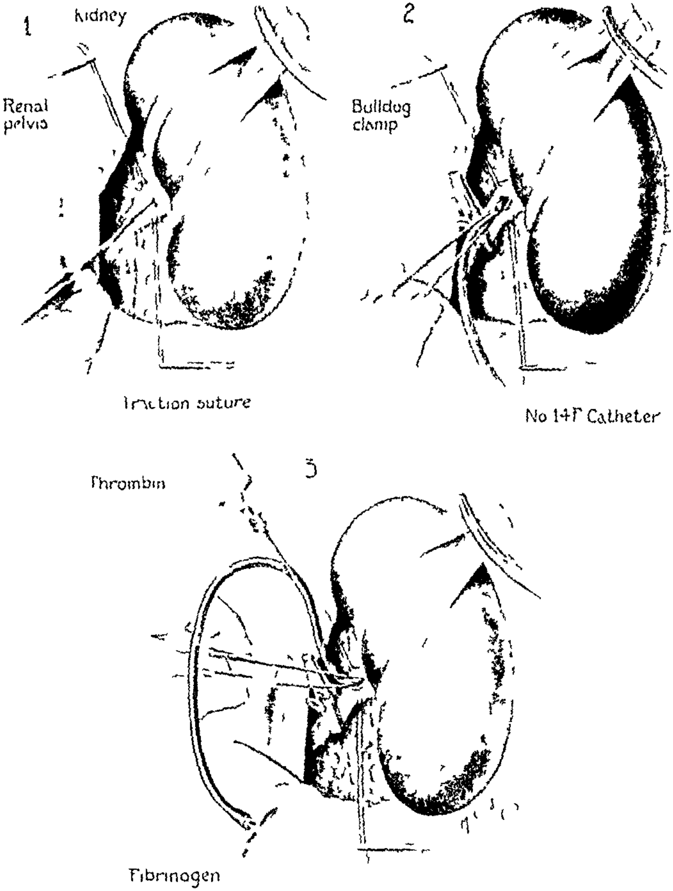

Fig 1 *1*, Exposure of upper ureter and preparation for incision of it, preliminary to coagulum pyelolithotomy Mobilization of kidney often is not necessary *2*, Catheter being inserted into opening in ureter, a rubber covered bull dog clamp has been applied to occlude ureter distal to opening *3*, Technique for simultaneous injection of fibrinogen and thrombin into renal pelvis is shown

is occluded distal to the opening by a rubber covered "bull dog" clamp. The catheter must fit snugly in the ureteral incision to avoid leakage The renal pelvis is emptied of urine and the catheter is adjusted so that it irrigates freely.

The capacity of the renal pelvis is measured by instillation of normal saline which is completely aspirated. Dees[5] has found the irrigation of the pelvis with a solution of 0.1 per cent Aerosol O.T. to be useful where considerable infection has been present in order to dissolve tenacious exudate binding calculi to the mucosa.

3) Fibrinogen[10, 11, 12] in solution in 0.15 M Na_2HPO_4 is injected into the renal pelvis to its maximum capacity and simultaneously human thrombin or clotting globulin (Lederle) is injected in one-tenth to one-fifth the volume of fibrinogen used by means of a different syringe into the lumen of the catheter as shown in figure 1, *3*. It is our custom for the operator to inject the fibrinogen solution into the catheter which is held in place by smooth forceps while the assistant injects the thrombin starting its instillation after 5 cc of the fibrinogen has been injected. After waiting for 5 minutes a firm clot has always been

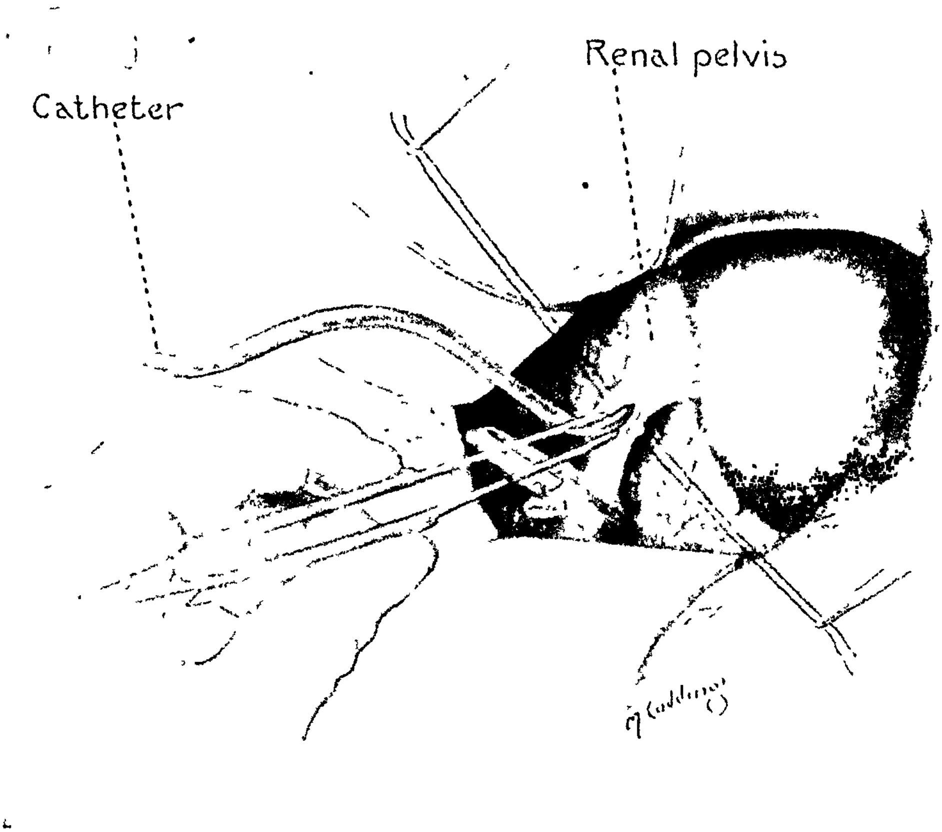

FIG. 2. Showing same technique as illustrated in figure 1, *2*, without mobilization of kidney.

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[10] Edsall, J. T., Ferry, R. M. and Armstrong, S. H., Jr.: Chemical, clinical and immunological studies on products of human plasma fractionation. XV. The proteins concerned in blood coagulation mechanism. J. Clin. Invest., **23**: 557–565, 1944.

[11] Ferry, J. D. and Morrison, P. R.: Chemical, clinical and immunological studies on products of human plasma fractionation. XVI. Fibrin clots, fibrin films, and fibrinogen plastics. J. Clin. Invest., **23**: 566–572, 1944.

[12] Morrison, P. R.: Preparation and properties of serum and plasma proteins. XV. Some factors influencing the quantitative determination of fibrinogen. J. Am. Chem. Soc., **69**: 2723–2731, 1947.

formed in the renal pelvis. Adequate distention of the renal pelvis can be easily determined by palpation.

4) The catheter is removed. Figure 3, *1* shows the enlargement of the opening in the renal pelvis to permit extrusion of the clot and adequate exposure for the removal of the coagulum and its contained calculi. The necessary size of the opening in the pelvis depends upon the size of the calculi present. Figure 3, *2* shows the removal of the coagulum with stone forceps. By moderately overdistending the pelvis with slightly more fibrinogen solution than the estimated volume, complete filling of all calyces with inclusion of all loose calculi is insured. Delivery of the coagulum is facilitated by spontaneous expulsion when pressure is released on opening the pelvis. After removal of the coagulum, digital exploration is necessary to search for adherent calculi and to identify calcified renal papillae. The pelvis is thoroughly irrigated with saline and a portable roentgenographic film of the kidney made. The opening in the ureter and renal pelvis is closed by loose approximation with 00000 catgut unless acute infection or significant chronic infection is present and the wound is closed in layers with interrupted cotton or silk sutures. The renal fossa is always drained through the posterior angle of the wound with a soft thin rubber drain.

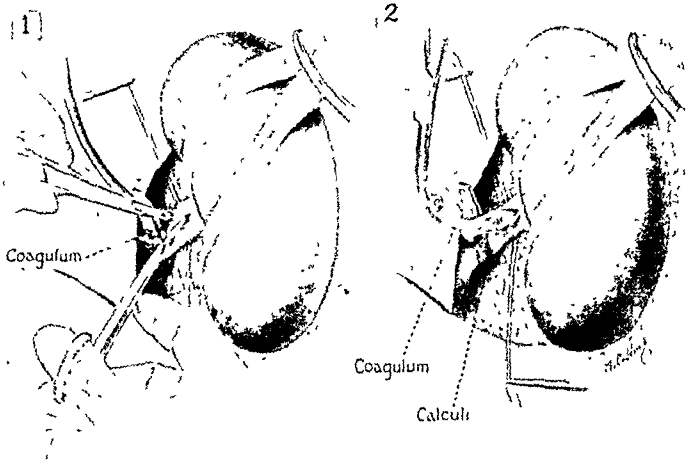

FIG. 3. *1*, Catheter has been remove [illegible] ing enlarged to permit removal of coagulum. *2*, Coagulum is [illegible] pelvis; size of opening [illegible] n is sho [illegible] ntaneous expulsion of opening is made, and this may be increased by manual com- [illegible]

Coagulum pyelolithotomy is not applicable to all cases of nephrolithiasis. Brief examples of the kind of case in which we have found it to be helpful follow:

CASE REPORTS

Case 1. A girl of 19 entered the Peter Bent Brigham Hospital because of recurrent attacks of left flank pain, chills, fever, frequency of urination and nocturia of three days' duration. In 1939, at the age of 11, division of an aberrant renal artery for left congenital hydronephrosis had been performed at another hospital. Three years later she was found to have 3 small calculi in the left renal pelvis. In 1943, one year later, clinical demonstration of 4 renal calculi was made but at exploration only two could be found. At the present admission in addition to evidence of pyelonephritis there was found 5 or possibly 6 opaque shadows in the region of the left kidney (fig. 4, *A*). An excretory urogram obliterated these shadows and showed a moderately dilated left renal pelvis apparently due to obstruction at the ureteropelvic junction (fig. 4, *B*). At exploration the left ureter and kidney were found to be bound down by dense adhesions causing extrinsic obstruction of the ureteropelvic junction. Mobilization of the upper one-third of the ureter could be carried out only by sharp dissection and relief of obstruction at the ureteropelvic junction was accomplished by lysis of adhesions. An incision was made in the upper ureter and coagulum pyelolithotomy carried out by the technique described above. Six calculi were delivered in the coagulum without disturbing the kidney (fig. 5). So adherent was the kidney that its mobilization would have been a major procedure in itself and could have been accomplished only by the subcapsular approach. It should be emphasized that an attempt 4 years previously had failed to remove 2 of 4 calculi present. It is also of interest that the preoperative diagnosis was definite for only 5 calculi and 6 were removed at operation.

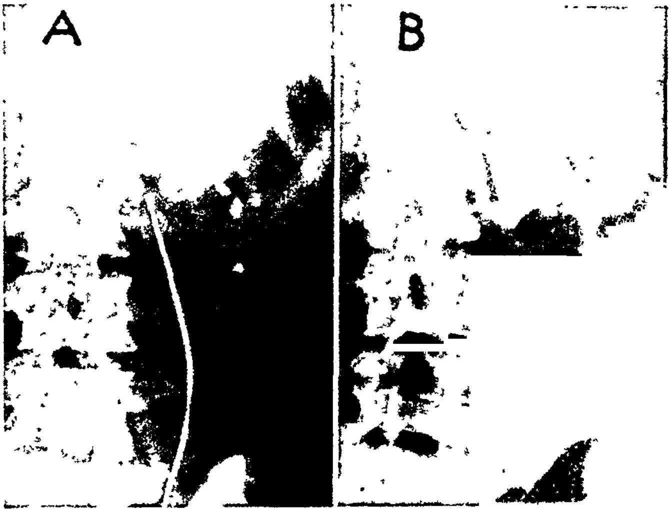

FIG. 4. Case 1. *A*, plain roentgenogram with ureteral catheters in place, showing 5 and possibly 6 opaque shadows in region of left kidney. *B*, excretory urogram at 30 minutes, showing moderate dilatation of renal pelvis, slight blunting of calyces, no filling of ureter, and all individual opaque shadows of calculi are obliterated.

Case 2. A male laboratory technician aged 48 was admitted to the Peter Bent Brigham Hospital for the treatment of hematuria, left flank pain, chills, fever (106 F), nausea and vomiting of 18 hours' duration. The patient was

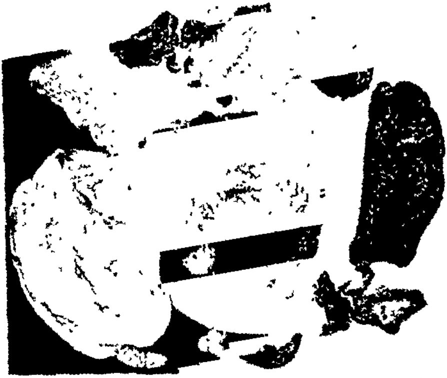

Fig. 5. Case 1. Photograph of operative specimen which consisted of coagulum and the contained 6 calculi.

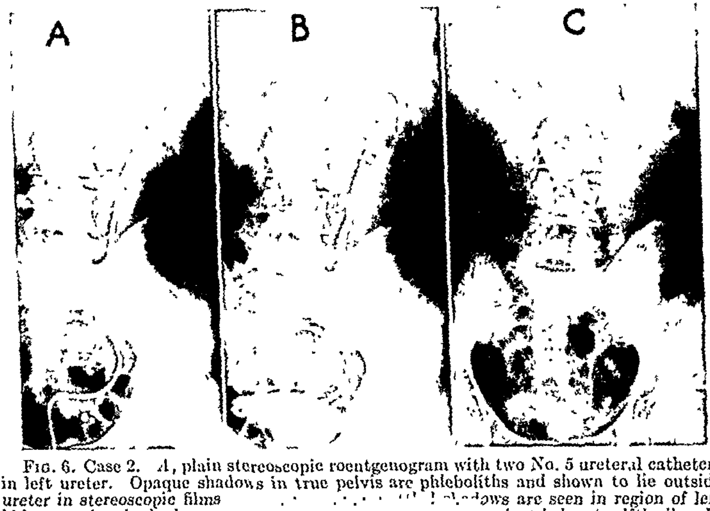

Fig. 6. Case 2. *A*, plain stereoscopic roentgenogram with two No. 5 ureteral catheters in left ureter. Opaque shadows in true pelvis are phleboliths and shown to lie outside ureter in stereoscopic films [illegible] shadows are seen in region of left kidney, and a single dense [illegible] en just below twelfth rib. *B*, retrograde pyelogram, show[illegible] ureter, negative filling defect of ureter, two dilated calyces and incomplete filling of renal pelvis. At operation these findings were found to be due to blood clot and multiple calculi. *C*, excretory urogram at 15 minutes 2 weeks after operation, showing good excretion from both kidneys with no blunting of calyces and only moderate enlargement of left renal pelvis. There is an opaque shadow outside the upper ureter which is thought to be a calculus that was expelled and lost when ureter was opened.

known to have arrested bilateral pulmonary tuberculosis and a chronic duodenal ulcer of 22 years' duration. For the latter he had taken large quantities of alkalies. He had passed a single calculus 8 years before the present illness. At cystoscopic examination the left ureter was found to be obstructed by blood clot. Two No. 5 ureteral catheters were passed to the left kidney and left in place for drainage (fig. 6, *A*). The next day a left retrograde pyelogram was made which showed a negative filling defect of the upper ureter and renal pelvis as well as two dilated calyces (fig. 6, *B*). The ureteral catheters became obstructed 48 hours after insertion in spite of repeated irrigations and operation was performed. The ureter, renal pelvis, parenchyma and perinephric tissues were found to be tense, edematous, and distended. No calculus was palpable; an incision was made in the upper third of the ureter just below the ureteropelvic junction and blood clot, much gritty material and an estimated 50 cc of bloody urine was expelled. The renal pelvis was irrigated with saline through a soft rubber catheter and this was followed by simultaneous filling with fibrinogen solution and thrombin (35 cc total). In 4 minutes a firm clot was formed and the pelvis was opened. The clot was easily delivered and found to contain much sandy material, small calculi, blood clot and a single stone 1½ cm. in diameter. Mobilization of the kidney was not deemed wise or necessary after further irrigation and exploration of the pelvis. A drain was placed in the renal fossa and the wound closed. Convalescence was uneventful. An excretory urogram was made 2 weeks later (fig. 6, *C*) which showed proper functioning of poth kidneys, relief of obstruction on the left and a single small calculus outside the ureter just below the renal pelvis which apparently had been forcibly expelled when the ureter was initially opened and had not been recognized.

This case demonstrates the use of coagulum pyelolithotomy in the acutely obstructed kidney complicated by infection, spontaneous hemorrhage and much calcareous debris which was nonopaque to the x-ray. It accomplished a more complete cleaning of the renal pelvis than could have been done by ordinary irrigations or instrumentation. The patient has continued to be free of signs or symptoms for one year since operation.

Case 3. A white man aged 46 was admitted to the Peter Bent Brigham Hospital because of an episode of left renal colic and hematuria which occurred 6 days before. The past history was significant in that 4 stones had been passed 26 years before, 6 had been passed 14 years before and 3 calculi 4 years before, all from the right kidney. At cystoscopic examination it was determined that bleeding was from the right kidney and roentgenographic examination showed that there was an irregular opacity in the lower major calyx (fig. 7, *A*). There was also evidence of infection in this kidney. Because of infection, pain and bleeding, operative intervention was deemed necessary. Coagulum pyelolithotomy was planned because of the intrarenal location of the only visible calculus and because of the history of repeated passage of multiple small stones in the past. This was carried out and an almost perfect mold of the renal pelvis composed of fibrin clot was delivered containing an irregular calculus which was apparently impacted in the infundibulum of a major calyx (fig. 7, *B*). This was accomplished without instrumental trauma to the kidney or to the calculus, which was soft and friable. A roentgenogram of the kidney at the operating table showed no residual fragments. A roentgenogram of the operative specimen (fig. 7, *C*) shows the contour of the coagulum and the calculus in striking contrast. The patient was discharged from the hospital 12 days later.

This case illustrates the effectiveness of coagulum pyelolithotomy in removing calculi located in a relatively inaccessible calyx. This stone could have been removed by instrumental means through a pyelotomy incision or by nephrotomy but either would have been more difficult and would have entailed trauma and possible bleeding. Many urologic surgeons have experienced at one time or another the chagrin of losing in the renal pelvis a calculus engaged in the ureteropelvic junction or upper ureter. By means of the coagulum these can be retrieved very easily without disturbing the kidney.

Case 4. A white woman aged 55 was admitted to the hospital because of pain in the right flank occurring intermittently for the previous 9 months. Eight years before she had suffered with similar pain in the left flank and had passed a urinary calculus. Cystoscopic and roentgenographic examination (fig. 8) showed evidence of an irregular calculus in the right kidney which was thought possibly to be more than a single stone and possibly in fragments. Coagulum pyelolithotomy was performed, resulting in the easy removal of a single irregular, large calculus from an intrarenal pelvis. This stone also could have been removed by simple instrumental means but again we were impressed with the ease of its removal without undue manipulation. The patient was discharged from the hospital with a well healed wound 11 days later.

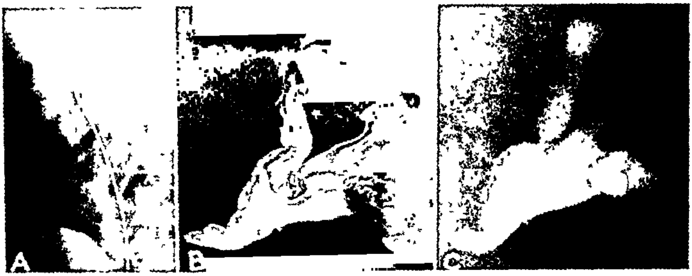

FIG. 7. Case 3. *A*, plain film with ureteral catheters in place shows small, irregular [illegible] of lower pole of right kidney. This is to be contrasted with roentgenogram shown in *C*. *B*, photograph of operative speci- [illegible] coagulum and calculus in infundibulum of lower calyx. This represents an almost perfect mold of renal pelvis. It has been found that those bits of coagulum left behind at operation are passed in urine within 48 hours. Clot does not retain its form for long in urine, and no difficulty has been caused by occasional postoperative passing of bits of coagulum. *C*, roentgenogram of operative specimen, showing detailed outline of calculus included in coagulum which is to be contrasted with preoperative roentgenogram. Coagulum itself is faintly opaque in vitro.

Case 5. A man aged 33 was admitted to the Peter Bent Brigham Hospital because of severe left flank pain of 7 hours' duration. A plain film showed an irregular, opaque shadow in the region of the left ureteropelvic junction and a retrograde pyelogram (fig. 9, *A*) demonstrated duplication of the left renal pelvis. As the opaque shadow had shifted in position on different occasions, a pneumopyelogram was made which showed the shadow to reside in the lower calyx of the lower pelvis (fig. 9, *B*). Preparation for operation was made with fibrinogen available

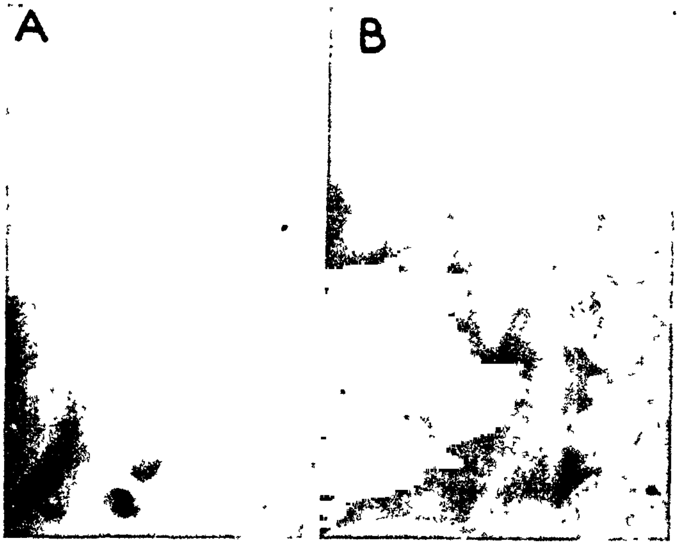

FIG. 8. Case 4. *A*, plain roentgenogram, showing large, irregular, opaque shadow in region of right kidney. *B*, right retrograde pyelogram, showing incomplete filling of middle and lower calyces and moderate dilitation of upper major calyx as well as irregular opaque shadow in pelvis extending to ureteropelvic junction of an intrarenal pelvis. This proved to be a single, irregular calculus which was completely delivered in fibrin coagulum by way of a ureterotomy opening without mobilization of kidney.

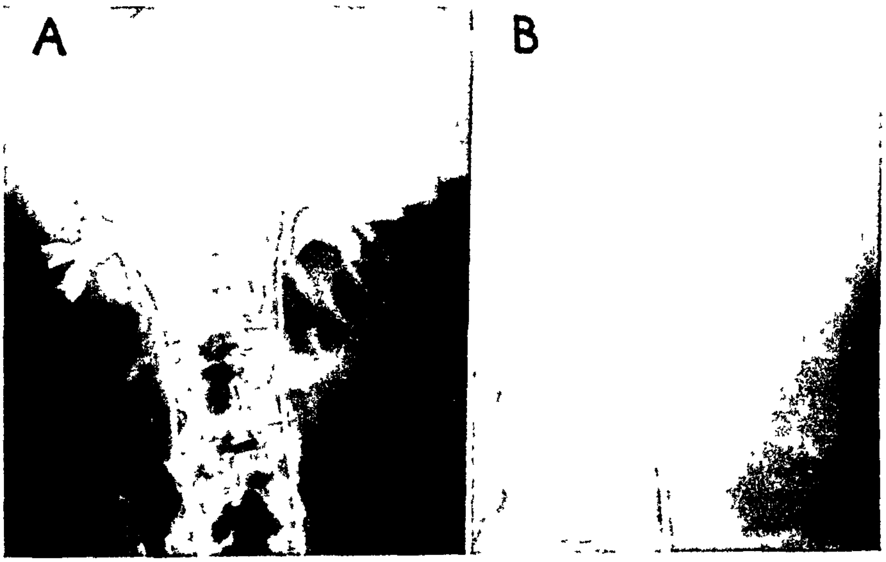

FIG. 9. Case 5. *A*, bilateral retrograde pyelogram, showing normal right renal pelvis and duplication of left renal pelvis. Opaque shadow in region of left ureteropelvic junction which was not shown on plain film is not seen. Patient had repeated attacks of left renal colic and hematuria. *B*, left pneumopyelogram, showing calculus which previously was in ureteropelvic junction now lies in lower calyx of left kidney. By means of fibrin coagulum technique, calculus was delivered through ureterotomy incision without mobilization of kidney.

for coagulum pyelolithotomy. The calculus was easily trapped and removed in the coagulum (fig. 10). Postoperative convalescence was uneventful and the patient was discharged from the hospital on the tenth day after operation.

A particular indication for this technique is illustrated in this type of case, namely that of the mobile roving calculus which may become impacted in the

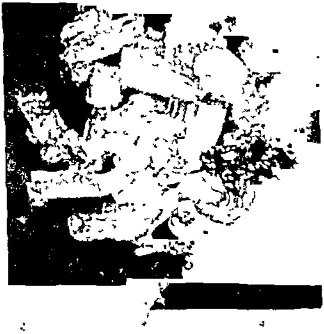

Fig. 10. Case 5. Operative specimen, showing multiple pieces of coagulum removed from renal pelvis along with [illegible]us which was drawn from lower calyx with aid of coagulum. [illegible] thrombin mixture, calculus was displaced from lower calyx [illegible] tion in ureteropelvic junction. Several small pieces of coagulum were passed in urine after operation.

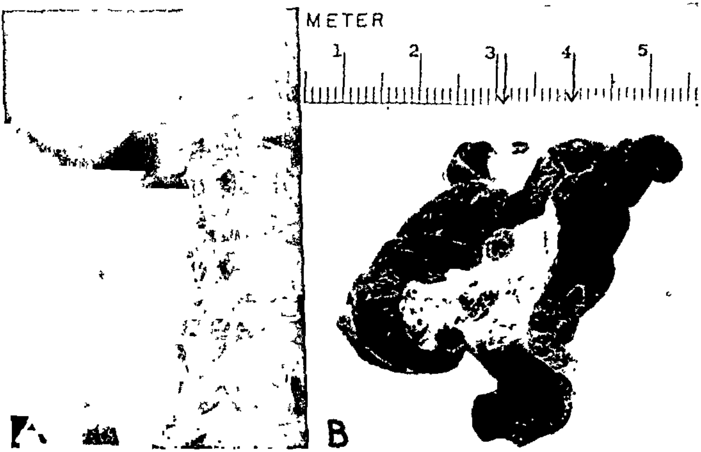

Fig. 11. Case 6. *A*, plain roentgenogram, showing irregular, opaque shadow in region of right kidney with a smaller linear opacity just below it. Retrograde pyelogram showed that these were in renal pelvis. *B*, photograph of operative specimen, showing large, irregular calculus surrounded by fibrin coagulum and 2 smaller calculi incorporated in coagulum. Only one of these was shown in roentgenogram made before operation.

ureteropelvic junction and then move back into the pelvis or one of its calyces. The coagulum technique often avoids extensive probing and exploring of the pelvis as well as possible nephrotomy incisions by trapping the loose calculi in its fluid menstruum which after clotting can be easily delivered or withdrawn by suction and irrigation. Once the surgeon has experienced the ease and facility of this procedure he will subsequently desire to have it available for use. Recently one of us entered an operation in which the resident had performed a ureterotomy for a stone in the upper ureter only to find that in spite of a bull dog clamp placed on the ureter above the stone that it had "slipped" into the renal pelvis. Fibrinogen was not available as the necessity for its use had not been anticipated; the renal pelvis was thoroughly irrigated and explored without finding the stone. A roentgenogram with the kidney mobilized revealed that the small calculus lay in a superior calyx. It was found by palpation and delivered with some difficulty and considerable bleeding. This case illustrates concretely the value of fibrinogen coagulum in pyelolithotomy for here it would have greatly simplified the procedure and avoided both mobilization of and prolonged exploration of the renal pelvis.

Case 6. A 23 year old man was admitted to the hospital with a diagnosis of renal calculi, right. Fifteen years ago the patient had 2 operations for sarcoid of the small bowel. In addition, at the age of 8, he suffered a cerebral-hemorrhage, complicating his recovery from his initial intestinal resection for sarcoid. He had residual hemiplegia and had been an invalid since that time. Nephrolithiasis was thought to be due to his prolonged bed rest.

Cystoscopic examination was carried out and he was found to have a colon bacillus infection of the right kidney. Roentgenographic examination (fig. 11, *A*) showed an irregular coral calculus in the pelvis of the right kidney and one small linear area of opacity thought to be another calculus. Coagulum pyelolithotomy was carried out. It was necessary to remove the large calculus and coagulum with the stone forceps. Two small calculi were included in the coagulum. Only one of these had been seen preoperatively. Figure 11, *B* is the operative specimen which shows the large calculus and two small calculi included in the coagulum.

Coagulum pyelolithotomy has been employed in 10 cases of nephrolithiasis; in 8 instances the technique was definitely helpful and facilitated delivery of calculi. In 2 cases the method was not successful or helpful; in one this was due to faulty technique and in the other failure was due to calculi being walled off in calyces in such manner as to be inaccessible to the coagulum and nephrotomy was necessary for their removal.

SUMMARY

Our experiences with the Dees' technique of coagulum pyelolithotomy have been discussed. Illustrations of this technique are shown and typical suitable cases described with roentgenographic and operative findings. The method has proven to be a definite contribution to the surgery of nephrolithiasis and represents a refinement of technique for selected cases. Its use is certain to become more widely employed as the materials become available through commercial channels.

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SPONTANEOUS PERIRENAL HEMATOMA ASSOCIATED WITH HYPERTENSION[1]

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Spontaneous perirenal hematoma is a comparatively uncommon pathological entity, particularly when associated with hypertension Therefore, we believe that a review of the literature to date, with a report of a case recently studied would be of value

REVIEW OF THE LITERATURE

In 1700, Bonet presented the first case on record He described a perirenal hematoma in a child suffering from an exanthem It was not until 1856 that Wunderlich described the disease fully and gave it a proper classification Spontaneous nontraumatic perirenal hematoma was then called Wunderlich's disease In 1910, Coenen coined the name perirenal hematoma and presented 13 cases. In 1933, Polkey and Vynalek reviewed the literature up to that time, and described a total of 178 cases Included in their review were both subcapsular and extracapsular hematomas, as well as renal and perirenal hemorrhagic cysts Since 1933, single cases have been reported by Coppridge, Carver, Heritage, and Pena-Martinez and Torriente We have found no mention of hypertension as a complicating factor in any of the cases reviewed

ETIOLOGY

The ages ranged from 6 to 89 years, with 70 per cent of the cases being between the ages of 20 and 60 Ratio of males to females was 3 to 2 In 18 5 per cent of the cases the hemorrhage was subcapsular and in 81 5 per cent it was extrarenal Causative factors in the order of their importance were as follows: trauma, diseases of the kidney such as nephritis, tumors, hydronephrosis, infections, tuberculosis, lithiasis, and cystic disease, blood vessel diseases, such as arteriosclerosis, aneurism, periarteritis nodosum, and renal infarcts, blood dyscrasias The mechanism of the hemorrhage is not definitely described, but increased intrarenal pressure is often mentioned as a factor

SYMPTOMOTOLOGY AND DIAGNOSIS

Symptomotology in general is rather indefinite unless the hemorrhage is sudden and profuse at the time of onset In that case, it is usually accompanied by severe pains in the affected renal area, and varying degrees of shock In addition, the history of trauma is often present in this type If the hemorrhage is slower, the only symptom is the gradual appearance of a mass which may not be noted until quite large This process may be so gradual as to lead to the comcidental finding of the mass, as was the case in the patient which we are presenting. Hematuria may be present, which, when associated with a mass in the kidney region, often leads to a mistaken diagnosis of renal neoplasm. X-ray of the abdomen frequently shows calcification in the hematoma and is one of the outstanding diagnostic features. There is usually some abnormality of the outline of the kidney pelvis on retrograde pyelography. Coenen found urinary tract disease in 53 per cent of his cases.

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[1] The paper is published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author

TREATMENT

Nephrectomy has been done in most of the recorded cases. In the acute unruptured subcapsular hematoma in which the hemorrhage has subsided the clots may be evacuated and the cavity packed. This has been done in a few of the cases.

In 1934, Goldblatt reported the temporary rise of blood pressure in dogs with experimental unilateral renal ischemia produced by partial obstruction of the renal arterial supply. In the case which we shall present, it is our belief that the hypertension is probably on the basis of a renal ischemia produced by prolonged marked perirenal pressure resulting in compression of the entire kidney.

CASE REPORT

A 34 year old white man entered the Veterans Hospital at Jefferson Barracks in October 1946. Careful questioning concerning past history with particular reference to urinary symptoms or the history of any trauma to either kidney failed to reveal anything of note. He stated that he might have had a mild injury while playing football, but that at no time was it of sufficient severity to require hospitalization or stop him from playing. There was no history of gross hematuria. His illness began in November of 1943, at which time he developed frontal and occipital headaches, marked dyspnea on exertion, and easy fatigueability. At that time the blood pressure was 230/130. He was hospitalized and later given a medical discharge from the Army. In 1944, he presented himself at a large medical clinic. His blood pressure was 220/140, for which a two stage bilateral sympathectomy was done. He was told by the surgeon that during the operation they had noted a large right kidney. Little relief was obtained from the sympathectomy, the lowest blood pressure recorded at rest postoperatively being 150/110.

He presented himself at Jefferson Barracks with two complaints; 1) general nervousness, irritability, and fatigue with dyspnea on exertion, and; 2) the inability to ejaculate after having erections. The latter complaint, of course, appeared after the sympathectomy. The only symptom referable to the kidney was a feeling of heaviness and slight aching in the right lumbar area, which had been present since early 1946.

The blood pressure on admission was 155/115. Eye grounds showed some narrowing and tortuosity of the blood vessels. In the right renal area, a nontender cystic mass was readily palpable, about the size of a large grapefruit. The nonprotein nitrogen was 31, and the urine showed no abnormality. Retrograde studies revealed a normal kidney both as to outline and function on the left side. On the right side, phenosulphonphthalein appeared in 5 minutes, with a 9 per cent excretion in 15 minutes. The urographic findings were very revealing (figs. 1 and 2). Figure 1 shows a large spherical calcified mass in the *right renal region, and after injection of the opaque medium one sees the renal* pelvis markedly compressed toward the midline with a certain amount of distortion, but with comparatively normal configuration of minor calyces. Figure 2 is a lateral view which demonstrates very well the large size of the mass and also shows compression of the renal pelvis. There is no obstruction at the ureteropelvic junction in either view. A diagnosis of subcapsular renal hematoma with calcification was made.

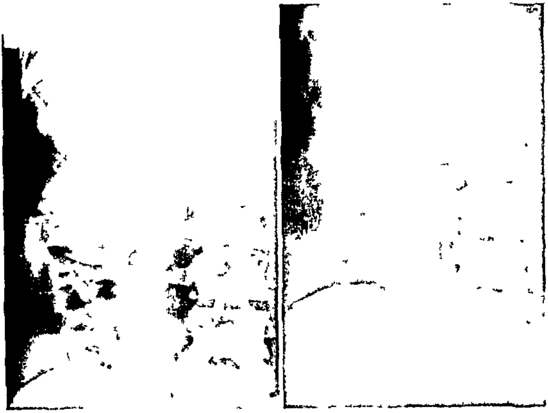

Fig 1.

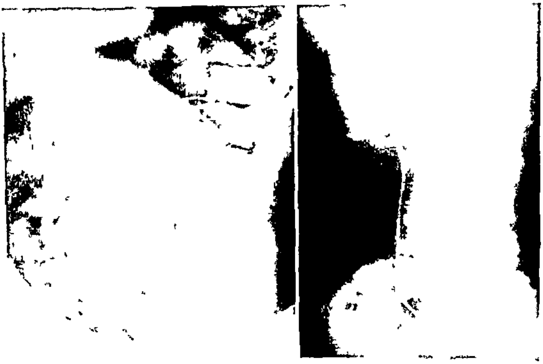

Fig 2.

Because of the large size of the lesion with which we were dealing, the kidney incision described by Hess, with removal of the twelfth rib, was used. Exposure was excellent throughout the procedure. Gerota's fascia was opened and there was considerable perirenal fat around the tumor. The lesion definitely did not involve the perirenal tissue and was obviously subcapsular in nature. The entire mass, including the right kidney, was easily separated from surrounding structures, the ureter and renal pedicle were ligated, and the lesion including the kidney removed.

Pathological specimen showed a large cyst which was markedly compressing the kidney substance. This cyst was thick walled in character and contained deposits of calcium which were readily palpable. The entire cyst was filled with a milky fluid in which were many shaggy organized clots. The specimen is shown in figure 3. Microscopic examination of the cyst wall showed hyalinized connective tissue with areas of calcification and osseous metaplasia.

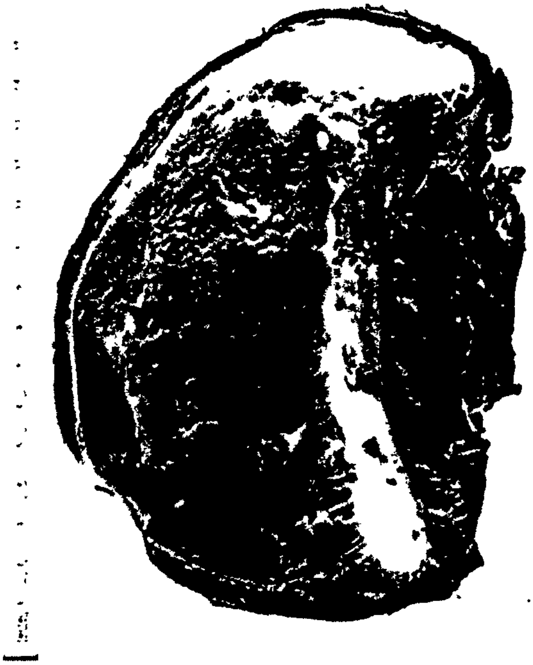

FIG. 3.

Immediate convalescence was uneventful. Blood pressure dropped immediately to 98/60 and at the completion of hospitalization was 124/72. The patient has been followed at intervals for 1 year during which time he has been quite active and carrying out his normal duties. Blood pressure readings are as follows:

	Date	*Blood Pressure*
Onset of illness	Nov. 1943	230/130
Before sympathectomy	Sept. 1944	220/140
After sympathetcomy	Sept. 1944	150/110
Before nephrectomy	Nov. 1946	160/108
After nephrectomy	Nov. 1946	98/60

	Date	*Blood Pressure*
Discharge from hospital	Dec 1946	124/72
Following discharge	Jan 1947	136/90
	Feb 1947	128/96
	Mar 1947	110/92
	Apr 1947	127/94
	Sept 1947	122/89
	Feb 1948	110/78

SUMMARY

The case reported presents true hypertension of renal origin which is undoubtedly due to the marked compression, by a large cyst, of a comparatively normal sized kidney with a normal blood supply Nephrectomy has produced what appears to be a complete cure of the hypertension

Spontaneous perirenal hematoma, particularly when subcapsular in nature, is a rare condition No definite causative factor was found in the case presented. As far as we have been able to determine, this is the only case of perirenal hematoma *with hypertension on record successfully treated by nephrectomy*

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VARIX OF THE RENAL VEIN: REPORT OF A CASE

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A Negress aged 31 years (L-46-235918) was admitted to Charity Hospital of Louisiana at New Orleans on October 22, 1946, complaining chiefly of pain in the upper right quadrant of the abdomen, radiating to the right flank with onset 10 days after delivery of her seventh child. With the onset of the pain the patient felt a hard, tender mass about the size of an egg, which seemed to lie just beneath the skin in the right flank. For 3 days the pain was intense and not relieved by morphine. Within 2 weeks the pain had decreased but then similar, less severe symptoms recurred. The past history was entirely irrelevant. She had had 11 pregnancies. System review was negative.

The admission temperature was 98 F, the pulse 76, the respiration 24, and the blood pressure 125/80. The following positive findings were recorded: The sclerae were slightly icteric. The breasts were enlarged and contained milk. In the upper right quadrant, just beneath the costal margin, there was a smooth, rounded, freely movable mass about 7 by 10 by 6 cm., which moved with respiration. There was generalized moderate tenderness in this area, with no point of maximum tenderness.

On the basis of her history, the patient was admitted to the surgical service with a tentative diagnosis of cholecystitis and cholelithiasis. Routine laboratory studies were reported as follows: Urinalysis revealed a normal urine. Urine culture yielded no growth. The total and differential blood counts and the hemoglobin value were within normal range. The blood serology was negative. The blood urea was 16 mg per cent. The icteric index was 6. The phenolsulphonphthalein excretion was 40 per cent in the first hour and 15 per cent in the second. Cholecystography and a gastro-intestinal series showed no abnormalities. However, the stomach and duodenum were observed to be pushed to the left.

The diagnosis of cholecystitis was discarded after physical examination had revealed the mass described. It was then thought to be an enlarged right kidney or a mass joined to the right kidney which displaced the stomach and duodenum.

Cystoscopy revealed no abnormalities. There was a 2 minute delay in the appearance of indigo carmine from the right kidney as compared with the left. Retrograde pyelograms (fig. 1) made at the time of cystoscopy showed the renal pelvis, the major and minor calyces, and the ureter to be normal on the left side. On the right, the renal pelvis was slightly larger than normal and none of the calyces could be visualized. The pelvis, apparently as the result of pressure, was divided into two distinct areas linked to each other by a small communicating lumen. The right ureter, except for some slight tortuosity, was normal. The impression was that the tissues in the lower portion of the right kidney were necrotic and had broken down, apparently because of pressure of a mass impinging upon the renal pelvis from its origin in the lower pole. The findings were considered compatible with cyst formation of the lower pole of the right kidney and operation was recommended on that diagnosis.

Operation (November 19, 1916, spinal anesthesia): When the right kidney was exposed through the usual nephrectomy incision, there was noted a marked enlargement of the right renal vein beginning 2.5 cm. distal to the vena cava and extending into the lower pole of the kidney. The vein was adherent to the renal artery but careful examination disclosed no vascular connection between the venous sacculation and the renal artery. Nephrectomy was performed without difficulty by the usual technique.

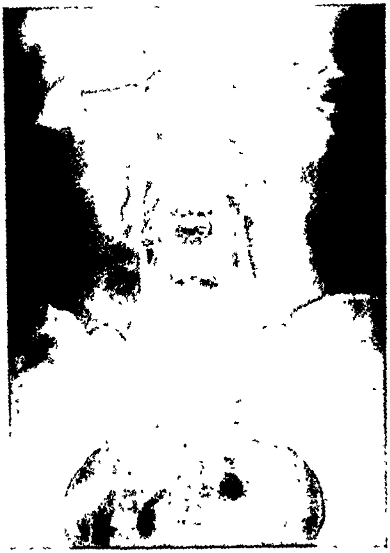

FIG. 1. Retrograde pyelogram, showing enlargement of lower half of right kidney, dilatation of pelvis and tortuosity of ureter. Note absence of calyces and division of pelvis as result of pressure defect.

When the specimen was opened at the point of dilatation, the vein was found to be filled with firm, dark red, clotted blood and a small amount of liquid blood.

Pathologic report (Dr. Holman): "The specimen consists of a kidney which measures 13.5 cm. from pole to pole, 6 cm. in width, and 3.5 cm. in thickness. It weighs 172 gm. The color is dark reddish pink. The calyces to the upper pole are markedly dilated and there is some atrophy of the pyramids in the region of the dilatation, which is most marked in the superior pole. The pelvis is slightly dilated. The renal vein shows a saccular dilatation (which has been opened) measuring 3 by 4 cm. (fig. 2). Accompanying the specimen are several fragments of firm, dark red blood clots. The lining of the vein is smooth and pink. In the proximal portion the lumen is considerably narrowed, though no cause for the change can be determined. The cortico-medullary ratio is preserved, the cortex measuring on the average 0.5 cm. in thickness. The medullary rays are prominent. The capsule strips with some difficulty. When it is removed, there is seen a somewhat granular surface with numerous small stellate scars. The ureter is dilated and thin. The mucosa is hemorrhagic in some areas.

"Sections of the kidney examined under the microscope reveal some dilatation of Bowman's capsule and some dilatation of the convoluted tubules and the collecting tubules. No casts are noted, but there is some cloudy swelling of the tubular epithelium.

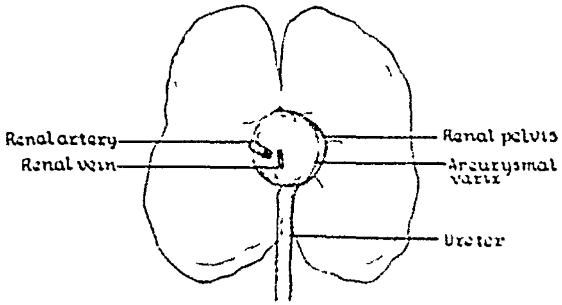

Fig. 2. Showing relation of varix of right renal vein to renal pelvis, artery, and ureter

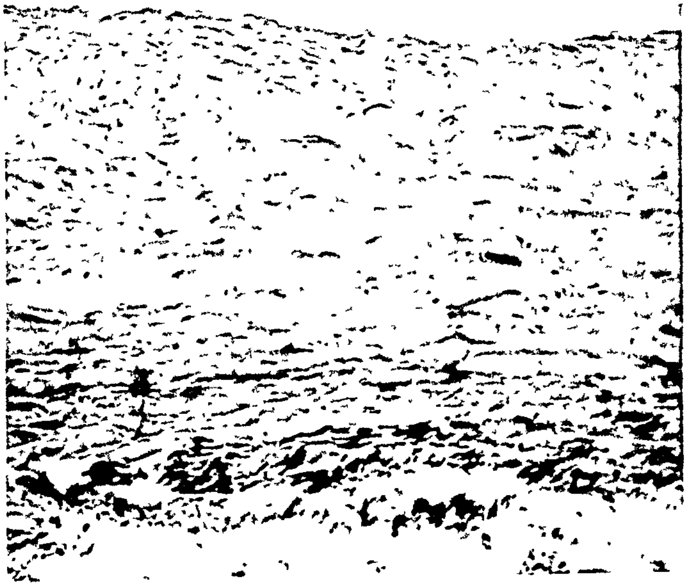

Fig. 3. Section through venous sacculation (X 100). For description, see pathologic report

"Sections of the sacculation (fig. 3) show a smooth endothelial lining. In one section (not shown) a delicate streak of fibrinoid material overlies the endothelium. The media is greatly thickened and hyalinized. In some areas large hyaline plaques almost completely obliterate any semblance of the former venous wall. In better observed areas (fig. 3) the smooth muscle fibers and remnants of the elastic framework are widely separated by hyalinized tissue. The adventitia is thinned. There is practically no leukocytic response anywhere in the sections examined."

The pathologic diagnosis was "mild hydronephrosis secondary to varix of the renal vein."

The pathologist observed that the histologic picture was similar to that seen in marked varicosities in the saphenous and other veins.

Recovery was entirely uneventful. The patient was examined thoroughly 7 months after surgery and found to be free from symptoms and able to attend to all her duties. There was no change in her blood pressure. She was advised to report again for examination at 6 month intervals.

COMMENT

So far as the authors are able to determine, this is the first instance of a primary varix of the renal vein to be put on record. An examination of the available medical literature from 1887 to date under appropriate headings (varices and kidney varices, aneurysm and blood supply) reveals no reference to a previously reported case.

Although the pathologic process most closely related to the lesion present in this case would seem to be a varix of the renal vein secondary to a renal arteriovenous fistula, in this type of lesion there is a moderate-sized nonsaccular dilatation of the renal vein proximal to the site of the fistula. Careful examination at surgery showed no evidence of an abnormal communication between the artery and the vein. The case reported here was clearly a varix of the renal vein which developed independently of any other pathologic lesion. The sacculation was in the renal vein, just proximal to the kidney, and it extended into the renal substance, where the effects of its pressure accounted for the deformity of the pelvis evident in the pyelogram (fig. 1). The renal artery in our case was normal, and in cases of arteriovenous fistulas the dilatations of the renal vein are always between the fistula and the vena cava.

The etiology in the recorded case is obscure. Careful questioning of the patient elicited no history of trauma. The close chronologic relationship between delivery and development of symptoms with the appearance of the mass suggests a possible etiologic relationship, but nothing in the history or findings supports the theory. It is quite possible, moreover, that the mass had been present for some time and had not been noticed by the patient because of the abdominal enlargement due to pregnancy.

The symptoms in this case were entirely referable to the gastro-intestinal tract, and on the basis of the history the diagnosis of cholecystitis with cholelithiasis appeared warranted. It seems doubtful that the picture in this case is typical, or that the diagnosis of renal varix can be made before operation.

The position of the renal varix as revealed at surgery was such that pressure on the renal artery must have occurred. but there were no variations of any consequence from the level (125/80) noted when she was first examined.

SUMMARY

We record here a case which we believe to be the first reported case of a varix of the renal vein.

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UNCROSSED DOUBLE URETER WITH RARE INTRAVESICAL ORIFICE RELATIONSHIP: CASE REPORT WITH REVIEW OF LITERATURE

ANTHONY J. LUND

In complete ureteral duplication there is usually frontal crossing of the ureters before their termination in the bladder. This crossing commonly occurs a short distance below the pelvis of the kidney and again near the bladder (Braasch and Hager). The ureter from the upper or superior pelvis then enters the bladder medial and inferior to that draining the lower or caudal half of the double kidney. The following case report reveals exceptions to both of these rules; namely, lack of crossing and intravesical opening of the ureter from the upper half of the double kidney cranial to that of the other ureter. This latter intravesical relationship of ureteral orifice to ureteral orifice is sometimes referred to as "Weigert-R. Meyer Law", because it occurs so consistently (Meyer).

CASE REPORT

L. H., a white woman, aged 39, was admitted to the Dee Memorial Hospital, Ogden, Utah, on October 17, 1946, because of pain in the right flank. The patient stated that the pain had been intermittent for 3 or 4 years, was noted especially after eating, and was aggravated by walking.

The past medical history revealed that the patient had had rheumatic fever as a child, followed by rheumatic heart disease.

Physical examination presented a well developed obese female. By percussion the heart was found to be enlarged slightly to the left of the midclavicular line. No arrhythmia and no murmurs were noted. Tenderness was elicited over the right flank region.

Several urinalyses were reported as negative. Other laboratory examinations, including complete blood count, hematocrit, sedimentation rate, blood cholesterol, blood urea nitrogen, and blood uric acid were all reported as within normal limits. The electrocardiogram showed left axis deviation and cardiac hypertrophy. A gallbladder series showed a nonfunctioning gallbladder and a presumptive diagnosis of chronic cholecystitis was made. Cholecystectomy was then done, followed by the pathologist's examination of the excised tissue, who submitted a diagnosis of chronic fibrous cholecystitis. The postoperative course was uneventful and a follow-up examination 6 months after discharge revealed that the patient was free from flank pain.

Prior to surgery a cystoscopy revealed two ureteral orifices on the left, with one opening 4 to 5 mm. superior and slightly medial to the lateral opening (fig. 1). Retrograde pyelography was performed and the patient was found to have complete duplication of the ureter, with no frontal crossing on the left side. The ureter from the upper kidney was noted to enter the bladder cranial to the normal ureter and slightly medial to it (figs. 2 and 3, *A*). The urine from each was clear and the urinalyses were reported as negative. The right pyelogram appeared within the limits of normal, except for mild nephroptosis.

ETIOLOGY

Before a discussion can be made as to the nature of the development of these anomalies a comprehension of the embryology of the ureter is essential. This subject has been dealt with extensively elsewhere (Chwalla; Felix; Hawthorne; Mertz; Meyer; Pohlman) and only a brief recapitulation will be given here.

About the 5 mm. stage of growth of the embryo there appears a ureteral bud on the medial dorsal side of the wolffian duct. There is then noted a lateral migration of the bud to the lateral side of this duct. The movement of the bud is also somewhat caudalward, bringing its inferior portion adjacent to the lateral wall of the bladder. Dilatation of the common end portion occurs (about 10 mm.) producing two openings into the bladder, instead of the single wolffian duct. A common septum then exists between the orifices. Chwalla terms the caudal end of this septum a spur. The spur furrows and further separates the ureter from the wolffian duct. For a short time the opening of the wolffian duct lies medial and cranial to the ureteral anlage (12 mm. stage). This period is short and soon the wolffian duct migrates caudally *to a position medial, but inferior,* to the ureteral orifice. The caudo-medial movement continues until the final stage when the ducts terminate side by side in the posterior urethra, as the ejaculatory ducts of the male, and in the vestibule of the female as Gartner's ducts. During this development, due to the rapid growth of the bladder, the ureteral orifices are drawn cranially and laterally. It is generally agreed that a trigone is formed from the wolffian epithelium. Normally, according to Meyer,

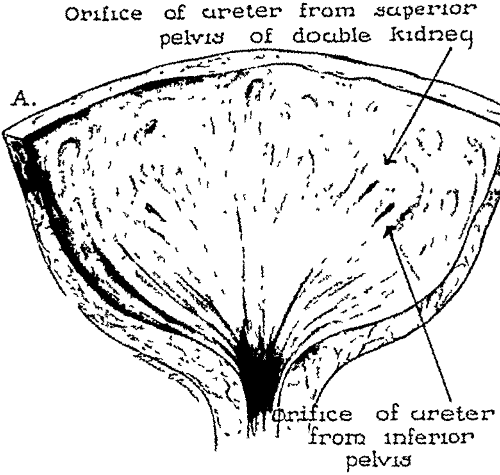
Orifice of ureter from superior pelvis of double kidney
A.
Orifice of ureter from inferior pelvis

FIG. 1. Artist's conception (after personally examining bladder with cystoscope) of location and relationship of ureteral orifices.

pared to other parts of the bladder. It is not beyond comprehension to conceive of the early medial orifice being caught in a wave of proliferation and pushed

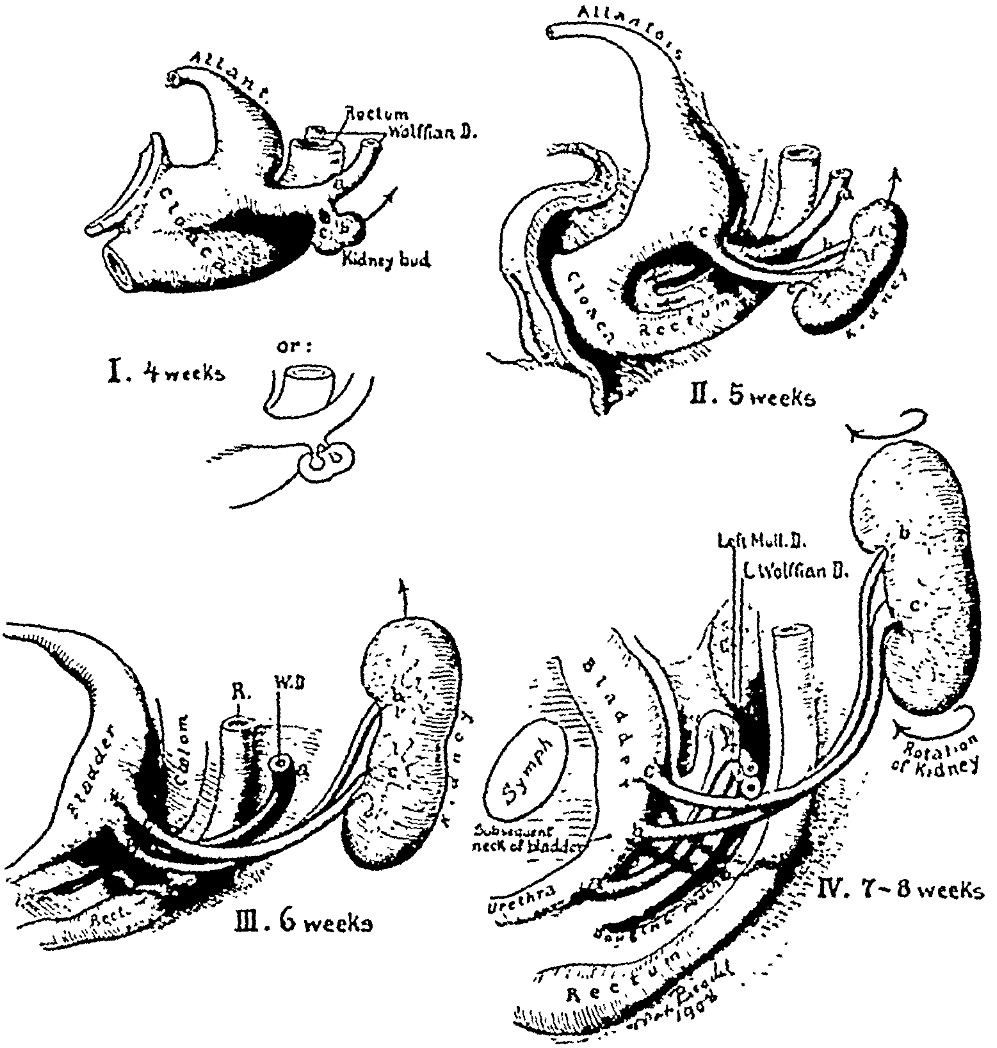

Fig. 4. Four diagrams illustrating development of a kidney with divided pelvis and double ureter. The figure shows why ureters cross and why upper pelvis and ureter drain into lower vesical orifice, while lower pelvis and ureter drain into upper vesical orifice. I, Double ureter starts from wolffian duct either *a)* as two separate anlagen *b* and *c)* or as an original single anlage showing a precocious branching which resembles a double anlage. II, Through expulsion of lateral portion of allantois, lower wolffian duct becomes dilated and lower ureter *c)* is first to reach allantois. Wolffian duct *a)*, carrying upper ureter *b)* with it, shifts with urogenital sinus in a downward direction, between allantois and rectum, as shown by arrows, until second ureter *b)* also becomes implanted in bladder, but farther down and more mesially than first, *c)*. III. We here see a continuation of same process of advance of wolffian duct with a greater separation of duct from ureter. IV, wolffian duct continues to travel downward with advance of urogenital sinus and finally becomes permanently lodged at neck of bladder *a)* in male; in female it continues still farther down. Last picture represents final arrangement, as seen in adult. Note that original order, *a*, *b*, *c*, as shown in first picture, is now reversed to *c*, *b*, *a*, at bladder." (After Kelly and Burnam, *Diseases of the Kidneys, Ureters and Bladder.* New York: D. Appleton & Co.; from Cabot's *Modern Urology*. Philadelphia: Lea & Febiger, 1936.)

slightly cranial to the lateral orifice, yet remaining within the confines of the trigone.

The explanation of the crossing of double ureters becomes simplified when one realizes that this crossing is only frontal (Meyer). Hawthorne described two contributing factors. Since the ureter to the superior pelvis reaches the bladder at a later stage, its opening is in a more caudal and medial location. This frequently produces a crossing just above the opening into the bladder. By the same token, if the ureteral outlets lie in about the same transverse position, or even cranial, crossing will be unlikely at this location. The other factor, and a more likely one, is that the lower ureter is more redundant, causing a loop or loops of this ureter to cross in front of the other. Redundancy and dilatation may be caused by obstruction and infection, as well as being of congenital origin (Herman). Conceivably then, the absence of redundancy by whatever cause may result in a double ureter without frontal crossing.

That redundancy is important in creating crossing has been shown clinically in the case described above. During cystoscopy the catheter leading to the upper kidney pelvis was pushed upward. A film was then taken and a crossing of the ureters is seen (fig. 3, *B*).

Braasch states that in some instances where there is apparent crossing the insertion of a catheter will separate the two ureters and crossing will not exist. That embryological development influences the sight of crossing is suggested by Weigert. He noted that completely duplicated ureters crossed where fusion occurred on the opposite side. This observation was made on 5 cases with complete duplication on one side and incomplete duplication on the other.

INCIDENCE

To date there have been only 2 other cases reported which violate the "Weigert-R. Meyer Law." Mills presented an example on the left side in a colored man and Kerr an example on the right in a white man. Both were found during postmortem examination. The ureters from the upper kidney pelvices entered the bladder slightly medial and cranial to the opening of the lower ureter in a manner similar to the case described above.

Geisinger, Salleras, Charrier, Braasch, Oraison and Tandonnet, Boechel and Franck, and other authors quoted by Stoeckel have presented cases of uncrossed double ureter. Were these case reports to represent the total incidence of this anomaly, it should be considered rare. However, Mertz reviewed a series of cases of ureteral duplication, in 13 there was specific mention of no crossing. One hundred forty-five cases of complete ureteral duplication were collected, making an incidence of approximately 9 per cent, which would suggest that the presence of uncrossed ureters in complete duplication is not rare. Unfortunately, Mertz was unable to inform the author of this paper which 13 of the 145 case reports were examples of uncrossed ureters so that they could be studied, nor did he mention whether they were clinical or postmortem findings. This latter fact is an important one to be considered as postmortem examination may distort the relationship of double ureters.

To substantiate Mertz's work, this writer (A. J. L.) collected from the literature 40 case reports of complete duplication of the ureter reported during the years 1916 to 1946. Five cases of the 40 were found in which illustrations of the urograms showed absence of crossing and were in living individuals. No mention was made in each report regarding the lack of crossing of the ureters. In order to verify the correctness of this observation, each author was written and it was concurred that in 3 of the cases crossing did not exist. Verification from the authors of the other 2 cases could not be had, because the original films had been destroyed.

Assuming all 5 to be examples of complete duplication of the ureter without frontal crossing, an incidence is noted of about 13 per cent. Disregarding the two unverified cases, the incidence would be about 8 per cent, which compares favorably with that of Mertz. It is not the intent of this paper to attempt to determine the exact incidence of uncrossed ureter in complete duplication; however, it seems reasonable to state that these findings are evidence that the presence of uncrossed ureters are more common than realized (in clinical cases) and the incidence possibly ranges from 8 to 13 per cent in completely duplicated ureters.

CLINICAL SIGNIFICANCE

One author states that in some cases one ureter may exert pressure upon the other at the site of crossing with resultant stasis (Mertz). If this be true, uncrossed ureters are free of this possible complication. Furthermore, if redundancy is an important factor in causing crossing, one might assume that an uncrossed ureter is more perfectly formed, or free of any acquired factors, which may cause redundancy. Meyer takes an opposite view. He feels that the absence of crossing is irrelevant and therefore this anomaly would have no more importance than any other type of double ureter.

Clinically, the intravesical orifice relationship of double ureters with one cranial and medial to the other has little or no significance.

SUMMARY

A case of complete duplication of the ureter without frontal crossing in which the ureter leading to the upper kidney pelvis opens cranial to the other ureter is presented.

The absence of frontal crossings is more common than realized (in clinical cases) and the incidence probably ranges from 8 to 13 per cent in completely duplicated ureters.

The presence of an intravesical opening of the ureter from the upper half of a double kidney, cranial to that of the other ureter, is an extremely rare finding. Two other cases have been found in the literature besides the one reported above.

The etiology and clinical significance of these two anomalies are discussed.

The author wishes to express his appreciation for the suggestions and criticisms made by Dr. George M. Fister in the preparation of this paper.

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this in 1927, consisting of heavy metals and arsenicals in large doses, according to his statement He admitted frequent indulgence in alcoholic drinks

The patient did not appear acutely ill Pupils were regular and reacted to light and accommodation Nose and ears were normal Teeth were in good condition There was no tremor of the tongue Chest was resonant throughout No rales were heard Heart was of normal size There were no changes in rate or rhythm or sounds The abdomen was distended with fluid The liver was palpable below the right costal margin The spleen was enlarged No lesions of the genitalia were present There were no abnormalities of size or of motion of the extremities The reflexes were physiological Temperature was normal

Urinalysis. specific gravity, 1 012, reaction, acid, albumin, 1 plus, no sugar, blood or casts, many leukocytes, red blood cells, 3,300,000, white blood cells, 7,600, hemoglobin, 57 per cent, small mononuclears, 35, transitionals, 2, eosinophiles 4, neutrophiles 60, total protein nitrogen 30 mg per cent, blood Wassermann was negative, spinal fluid was negative, abdominal fluid showed no growth after 3 days, phthalein test, first half-hour 10 per cent, second half-hour 15 per cent, second hour 30 per cent

An intravenous urogram revealed a good concentration of the dye in both kidneys after 5 minutes An x-ray of the lungs showed no evidence of pulmonary or pleural disease

Cystoscopy revealed no abnormalities

Examination of the gallbladder after oral administration of the dye failed to show outline of the gallbladder The gallbladder could not be visualized, probably because of poor excretion of the dye by the liver

Paracentesis of the abdomen revealed 3,000 cc of clear amber fluid While on the medical ward it was necessary to perform paracentesis every 3 weeks Mercurial diuretics had little effect during this last admission

On February 11, 1941 a right nephrectomy and anastomosis of the right kidney pelvis to the peritoneum were performed The right kidney was exposed The pedicle was clamped, cut, and ligated with No 2 chromic catgut ligatures The pelvis was then trimmed from the kidney It was anastomosed to the peritoneal gutter along side of the ascending colon This site was chosen with the view that the peristalsis of the colon would tend to keep the anastomotic opening swept free Intestinal catgut sutures were used in the anastomosis A circular opening about 2 cm in diameter was made in the peritoneum Interrupted black silk sutures were used in the outer layers The wound was closed with one cigarette drain to the site of the kidney pedicle The wound was closed in layers of No 2 chromic catgut and silk worm stay sutures

The patient's condition was satisfactory following operation However, infection developed at the wound site in a few days The bladder output increased to an average of 1300 cc in 24 hours The voided urine was cloudy, dark amber, and contained albumin The wound infection cleared up After 3 weeks the bladder output fell to the usual preoperative quantity of 400 to 600 cc The abdomen again began to fill with fluid

The bladder was flushed 3 times with 1-4000 alkaline *mecuric cyanide* solution and 3 times with sterile normal saline. A ureteral catheter was passed up the anastomosed ureter. The catheter tip encountered obstruction at the site of the anastomosis. The wound was reopened. The ureter and pelvis were in good condition. The opening was found to be blocked by adherent omentum and adhesions to the wall of the ascending colon. Ascitic fluid (3000 cc) was evacuated. The omentum and adhesions were cleared from the anastomosis. The wound was closed as on previous occasion. Drainage continued satisfactorily into the bladder for one week and again ceased. Eleven days after the second operation the bladder was treated as before. A ureteral catheter passed readily into the peritoneal cavity, and clear amber fluid (4600 cc) was withdrawn.

We concluded that the ureter was remaining patent but that the site of the anastomosis was wrong. The assumption that the peristalsis of the colon would tend to keep the opening clear and that the omentum would not interfere was wrong. The drainage was intermittent for the next two weeks.

On April 17, 1941 the wound was again reopened. It was moderately fibrotic over the ureteral opening. The ureter was freed. The fibrotic end was excised and split. A new peritoneal anastomosis was made directly behind the lower part of the right rectus muscle. The split ends of the ureter were sutured with fine intestinal catgut. The wound was closed in layers.

The patient recovered rapidly. The anastomosis continued to function satisfactorily. He was purposely held in the hospital until December 17, 1941. The vesical output averaged 1300 to 1500 cc per 24 hours. Ascites has not occurred. During the past 7 years he gained in weight and strength and worked satisfactorily as a steward on army transports during the war.

Figure 1 shows a profile of the patient before and after the last operation. The photograph of the x-ray film shows the retrograde injection of Diodrast in the transplanted ureter shortly before his discharge from the hospital (fig. 2).

The patient has continued to report to the hospital for observation up to the present time (fig. 3). He was recently admitted to the hospital because of diabetes mellitus. This condition is under outpatient treatment at the present time. He has had no recurrence of ascites to date.

The following abstracts were on patients with more advanced disease. The outlook was not so favorable as with the first patient.

The autopsies reveal the character of healing obtained.

The following patient died as a result of peritonitis, which must be attributed to faulty technique.

Register No. 111360, a white man, aged 55, entered the hospital February 10, 1943 on the medical service complaining of swelling of the stomach, legs and of hernia. He stated he had been well except for the last 6 years when he had been troubled by hemorrhoids. Three weeks ago he began having gas over the stomach, constipation, and dark bloody stools. For the past 1½ weeks there had been marked swelling of the legs and the abdomen. This had produced shortness of breath. Five days prior to admission he was compelled to stop work. He lost about 18 pounds in the last few weeks prior to admission and his appetite

FIGURE 1

FIGURE 2

was poor. He had been accustomed to taking about 3 drinks of spiritous liquor about 3 times a week and about 6 or 7 glasses of beer a week. Family history had no bearing. He denied all previous illnesses, operations, and venereal disease.

The patient was poorly nourished, and slightly dyspneic. He had marked abdominal enlargement; the skin was dry; mucous membranes were pale; no lymphatic enlargement; pupils were round and reacted to light; he was edentulous; the heart appeared to be displaced upward to the left; the rate was 84 per minute and regular; the diaphragm was displaced upward; the lungs were resonant with a few crackling rales; the abdomen was markedly distended with fluid; the skin was tight; there was a left indirect inguinal hernia; there was marked pitting edema of both legs; the reflexes were physiological; external hemorrhoids were present; the prostate was slightly enlarged. The blood pressure was 118/80; total protein 7.6 per cent; A-G ratio, total albumin 1 per cent, globulin 6 per cent; Wassermann is 1 plus; Kahn negative; the blood picture showed: 4,490,000 red blood cells, 8300 white blood cells, 16 gm. hemoglobin, 24 per cent lymphocytes, 7 per cent transitionals, 2 per cent eosinophiles, 66 per cent neutrophiles; blood nonprotein nitrogen 38 mg. per cent; urinalysis acid; no sugar; 1.027 specific gravity.

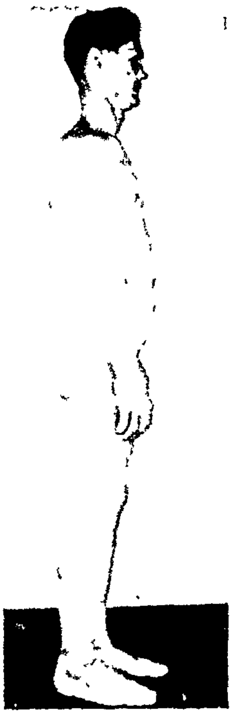

FIGURE 3

A paracentesis of the abdomen was done; no malignant cells were found. Cell count revealed 369 red blood cells per cubic millimeter; 15 white blood cells. A gastro-intestinal series showed no evidence of organic disease of the stomach or duodenum; there was no evidence of metastasis of the lungs or ribs. 6½ liters of fluid were removed at the first paracentesis February 11, 1943; 11,000 cc were removed March 5. An intravenous pyelogram on May 16, 1943 showed fair renal function of both kidneys.

May 24, 1943, because of the poor prognosis an exploratory laporatomy was performed. This revealed marked cirrhosis of the liver. A left nephrectomy was performed. The left ureter was brought forward and anastomosed directly behind the left lower rectus to the peritoneal cavity. A No. 7 F Vinelyene plastic catheter was passed through the ureter and down to the bladder with the idea of drawing it on out the urethra. The omentum was sutured away from this anastomosis. One cigarette drain was placed in the kidney pedicle. It is noted that the liver was about one-third the normal size and of orange-yellow and nodular throughout.

He was not considered a good subject for surgical treatment. He expired on May 27, 1943, 3 days following operation, of general peritonitis.

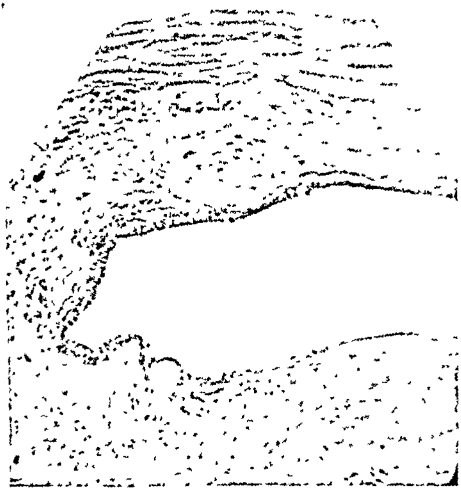

FIGURE 4

It is believed that the change in technique of passing the ureteral catheter from the peritoneal side to the bladder was faulty although this was drawn out through the bladder immediately after the return of the patient to his bed. It was found at autopsy that urine had apparently run up this catheter from the bladder to the peritoneal cavity, during time of removal to the ward. This appeared to be the source of the peritonitis. A urethral catheter was placed in the bladder at the time the urethral catheter was withdrawn through the ureter.

The autopsy afforded an opportunity to study the healing of the anastomosis (fig. 4).

Register No. 176483, a white man, aged 61, was transferred to this service from the medical service on February 26, 1947 for a palliative operation for his ascites. He had advanced cirrhosis of the liver of Laennec's type. There were varices of the esophagus. Exploratory operation revealed the liver to be about one-third the usual size. The spleen was moderately enlarged. The liver was nodular and orange-yellow color. The abdomen was filled with ascitic fluid.

As a palliative measure the left kidney was removed. The ureter of this kidney was then anastomosed to the peritoneal cavity. The patient's abdomen remained flat. The operation was successful in relieving the ascites. The wound healed *per primam.*

During the last week of illness there were repeated hemorrhages from the varices about the lower end of the esophagus. He vomited blood and passed large amounts per bowel. He received transfusions of blood and infusions of glucose. The abdomen remained flat since the operation.

Patient died at 4:22 p.m. on April 2, 1947. The primary cause of death was cirrhosis of the liver. The contributory cause of death was considered to be hemorrhage from the engorged veins about the esophagus.

Autopsy showed no peritoneal reaction. The abdomen was free of fluid. The anastomosis was patent and healing satisfactorily.

Register No. 153285, a white man, aged 44, was admitted to the hospital July 27, 1945 with complaint of enlarged abdomen and swelling of the knees, ankles and scrotum. He had difficulty in breathing. He dated the sudden swelling of the abdomen from June 1, 1945, following which the ankles and knees and then the scrotum became swollen. He consulted a physician June 8, 1945. He stated that a paracentesis had been performed and about a gallon of fluid had been removed. He stated he was tapped 5 times within 31 days. The swelling recurred.

He admitted drinking about 2 to 3 quarts of liquor per 24 hours. He stated he did not eat while ashore when drinking. These were the first symptoms of this character he had noticed. He believed he had consumed 2 or 3 quarts of whiskey a day for the past 25 years. He smoked one pack of cigarettes a day; no other drugs. His mother had died of pneumonia; his father from an accident. His last tropical service was in 1943 in New Caledonia. He had a broken left elbow; had metal fragments back of right shoulder in 1942 and a burn of the right leg. He denied veneral disease for the past 20 years.

Physical examination showed no abnormalities about the head. Hearing was fair. The teeth were in poor shape. The chest was resonant; no adventitious sounds were heard. The abdomen was distended and had a percussion wave. There was no complaint of the intestinal tract. The scrotum was edematous. He had no urinary complaints. Extremities revealed a moderate amount of edema; no palpable disease per rectum; the back was normal; the blood pressure was 100/60; the weight was 200 pounds; reflexes were normal; sedimentation rate was 23 mm. in 1 hour; the ascetic fluid revealed no abnormal cells; blood non-protein nitrogen was 33 mg. per cent; Mazzini and Kahn were negative; plasma protein 6.2 gm. per cent; icteric index was 12; urinalysis was acid; there was no albumin and no sugar; a few urates per high power field; the blood picture showed 3,900,000 red blood cells, 12,200 white blood cells; hemoglobin 12 gm.; 16 per cent lymphocytes; 6 per cent monocytes; 4 per cent eosinophiles; 72 per cent neutrophiles; 2 per cent bands; the culture of ascitic fluid was negative; there was a negative cephalin flocculation, culture for tuberculosis from the fluid was negative, the AG ratio was 2.5 per cent albumin to 2.85 globulin.

The clinical diagnosis was cirrhosis of the liver, atrophic type, with portal obstruction and ascites.

Intravenous pyelogram revealed fair function of both kidneys. He required a paracentesis of the abdomen every 7 days. At each occasion about 27 pounds of straw-colored fluid were removed.

On January 18, 1946 a palliative operation was performed to relieve the recurring ascites. The liver was about one-third normal size. It was typical of Laennec's type of cirrhosis. The spleen was fused to the parietal wall. The left kidney was exposed. Aberrant vessels at the upper pole were clamped and ligated, following which the renal vessels were doubly ligated. The kidney was removed and the pelvis was anastomosed to the peritoneal cavity directly behind the sheath of the left rectus. A vitallium tube was placed in the opening of the ureter and pelvis of the kidney to maintain the patency. The peritoneal cavity was closed with interrupted chromic catgut. The walls were closed with black silk stay sutures. One rubber tube drain was sutured in the abdominal cavity at the upper end of the wound. A Penrose drain was placed in the left kidney pedicle and the skin was closed with silk. The hemorrhage was slight, no shock.

The patient maintained a good recovery from the operation. Paracentesis was necessary on four occasions following the operation January 28, March 1, March 18, and March 27. This was believed due to an abscess which developed at the site of implantation. This abscess was incised and drained. The patient had no symptoms following this procedure.

He returned to work April 29, 1946 in a saloon. Epididymitis which developed on the left side resulted in atrophy of the testicle. It is believed that the clamping of the spermatic vessel on this side was partially responsible for the atrophy. He felt well and gained considerable weight and had put on a large amount of subcutaneous fat.

The patient re-entered the hospital November 17, 1946, stating that he had been at home completely anuric for the past 5 days. He was lethargic, had headaches. Catheterization revealed the bladder to be empty of urine. He admitted that he had been working at night in a saloon and that he had not taken any fluids. He denied any return to his drinking habits.

Catheterization was performed. Two 6 F catheters passed readily to the right kidney level. About 40 cc thick cloudy urine were obtained. An x-ray film did not reveal any obstructive calculi.

The blood nonprotein nitrogen was reported as 36 mg per cent.

Following catheterization he left the hospital against advice. He reported back to the hospital December 3, 1946, stating that he was feeling all right and voiding well. B proteus was cultured from the urine. He had never required paracentesis since his time of hospitalization and operation in January 1946.

It is believed that his ahydria, together with some abdominal pressure, was responsible for the acute obstruction to the remaining right kidney.

He returned to the hospital December 24, 1946. At this time there was evidence of gastro-intestinal hemorrhages from varices of the esophagus. The bleeding continued. He lapsed into coma. About 80 cc of cloudy urine was obtained from the right kidney pelvis. The blood nonprotein nitrogen rose to 150 mg. per cent. The patient continued to bleed from the mouth and passed a large amount of blood from the rectum. He expired January 1, 1947.

The operation he had received was successful in relieving the ascites. The cirrhotic condition of the liver was progressive. The cause of death was hemorrhage from the gastro-intestinal tract.

Register No. 178146, a white man, age 62, was first admitted to the medical service in January 1947 with symptoms of cirrhosis of the liver, ascites, arteriosclerotic heart disease, with auricular fibrillation. He also had a cystadenoma of the thyroid. Exploratory laparotomy revealed a cirrhotic liver.

A vitallium tube was used to anastomose the peritoneal cavity to the abdominal wall in order to secure drainage of the ascitic fluid. This relieved the patient for a short time. Then, for reasons which were not discernible, the ascites returned. He re-entered the hospital April 1, 1947.

On May 14, 1947 he received an anastomosis of the left renal pelvis to the peritoneal cavity. It was found that the vitallium tube, formerly placed as a connection between the peritoneal cavity and the tissues of the abdominal wall, had slipped back into the peritoneal cavity where it was hanging free by its attached black silk suture. Considerable fibrosis was found around the left kidney at the time of operation. The patient made an uneventful recovery. He was considered a poor surgical risk at the time of operation.

This patient received crude liver extract by vein before and after operation. He appeared to have responded well to this treatment. The administration was carried on 3 times a week. Crude liver extract (20 cc) was injected intravenously into 500 cc of saline and allowed to drip slowly by vein.

The patient's total protein before operation was 6.3, albumin 4.1, globulin 2.2. Total protein in ascitic fluid was 4 per cent. In July 1947, as a follow-up, the total protein in the blood plasma was 6.7, albumin 2.6, globulin 2.1.

CONCLUSION

These case histories have been presented with a view of showing that it is feasible to obtain relief from ascites by anastomosing the ureter to the peritoneal cavity. The selection of cases depends upon the degree of cirrhosis. If the patient is nearing complete hepatic insufficiency, no operation is tolerated well.

The technique is simple. Nephrectomy and sacrifice of the kidney are the major parts. The passage of a ureteral catheter after about 10 to 12 days is advisable in most instances, after irrigation of the bladder with an antiseptic followed by sterile water or saline. The operation is of palliative nature only to relieve the patient of the accumulation of fluid.

The last patient to receive this operation is being treated by the intravenous use of liver extract according to the method outlined by Labby. I believe that accessory treatment of this character will become standard practice as it is necessary to maintain the liver function.

The question naturally arises that a considerable amount of protein is drawn off through the bladder. Among the cases that we have checked before and after operation, the operation does not appear to have altered the plasma protein to any great extent The protein which is present in ascitic fluid probably is of no value to the patient as such when in solution in the ascitic fluid

It is essential to prepare these patients as well as possible before operation and to continue treatment for the cirrhotic disease of the liver after operation

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URETERAL REFLUX IN THE NORMAL CHILD

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The question as to whether ureteral reflux does or does not occur in the normal urological tract has received considerable attention and discussion in the past. However, no definite proof has been offered on either side of the question. In children in particular, the status of ureteral reflux is uncertain. This investigation was undertaken in an effort to find out if ureteral reflux did or did not take place in the apparently normal child's urological tract.

It has been shown that for the most part the intravesical portion of the ureter acts as a very effective valve, preventing the backflow of any fluid from the bladder into the ureter. Gruber in 1928 showed that the excised human urinary bladder could be filled to the bursting point without increasing the intra-ureteral pressure. In 1929 he illustrated that in animals, the percentage of ureteral reflux varied inversely with the thickness of the bladder wall, i.e., the intramural portion of the ureter. In animals with thin bladder walls, reflux occurred up to 80 per cent; as animals with thicker bladder walls were used, the incidence decreased toward zero.

Prather reviewed the literature up to 1944 on the subject and found a wide divergence of opinion among leading urologists. Some stated that reflux did not ever occur in the normal tract. At least one authority stated that it did occur. Campbell reviewed several hundred cystograms done on children because of various urological complaints or findings. From these he concluded that reflux did not occur in the normal child's urological tract.

EQUIPMENT AND METHOD

The equipment necessary to do the cystograms was simple and consisted of a 50 cc Luer syringe with a loose, easily moved cylinder. A selection of rubber urethral catheters and a supply of 4 per cent sodium iodide or other suitable radio-opaque medium completed the set up.

The method of doing the cystogram was equally simple. No anesthesia, local or general, was used. After the genitalia were cleaned, an appropriate sized rubber urethral catheter was inserted and all the urine drained from the bladder. The radio-opaque solution was then injected with the 50 cc syringe until the back pressure was sufficient to cause the plunger of the syringe to move backwards. The x-rays were taken at this point; one or more anterior-posterior films being exposed, being sure that the film included the kidney region. In about one-half the cases, the catheter was removed before taking the x-ray. Cystometric determinations were done on 12 cases to check the bladder capacity. Almost identical results were obtained by both methods.

TABLE 1. *Summary of cystographic findings on 43 children with no urinary complaints or signs*

A. 39 children—negative findings.
B. 4 children—positive findings.

CHART NO.	AGE	SEX	REASON FOR ADMISSION TO HOSPITAL	CYSTOGRAM
864553	10 wks.	M	Feeding problem ? Idiocy	Small diverticulum on left side dome of bladder
605011	10 yrs.	M	Left cryptorchidism (only undescended testicle in series)	Two fair sized diverticula, one just above either ureteral orifice
846357	13 mos.	M	Upper respiratory infection	Reflux up rt. ureter filling pelvis, outline of bladder, ureter and pelvis normal
891580	16 mos.	F	Inguinal hernia	Reflux up rt. ureter filling pelvis; outline of bladder, ureter and pelvis normal

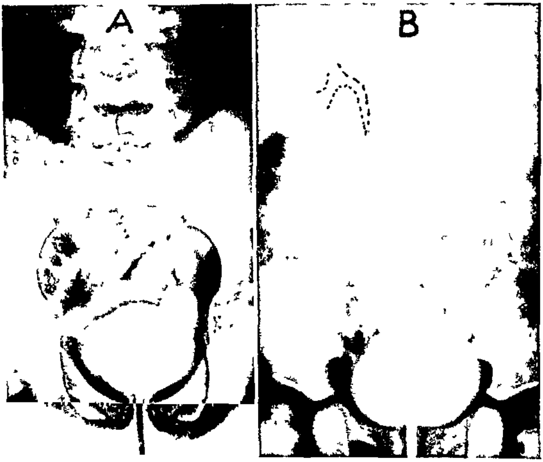

FIG. 1. *A*, cystogram on 10 year old boy, showing bilateral diverticula of bladder. *B*, cystogram on 13 month old boy, showing reflux up right ureter. (Outlines have been added for sake of clarity.)

MATERIAL

Forty-three children were selected of both sexes and varying ages up to 12 years. These children had no urological complaints or findings, and in all the urine was negative. These patients had been admitted to the hospital for various reasons such as fractures, swallowed foreign bodies, burns, etc.

The cystograms were done after the children had recovered and were about ready to go home.

RESULTS

From the 43 cystograms done on children without urological complaints or findings, 2 cases of ureteral reflux and 2 cases of unsuspected bladder diverticula were discovered. The results are summarized in table 1. Figure 1, *A*, shows the case with bilateral diverticula; figure 1, *B*, one of the children who had ureteral reflux.

DISCUSSION

The finding of 2 cases of vesical diverticula was incidental to the main purpose of this investigation and is reported as such. However, the child with the two diverticula was cystoscoped, and a definite median bar type of obstruction was encountered at the bladder neck. Consent could not be obtained to cystoscope the other child who had a diverticulum.

Of the two children showing ureteral reflux, both were quite young: one, 13 months; the other, 16 months old. One child was a male; the other a female. Both showed reflux on the right side. These two children were not cystoscoped, but there were no urinary complaints; the urine was negative and on x-ray, the bladders were normal. Also, the ureters and the pelves of the kidneys appeared perfectly normal, there being no dilatation, kinking, or other abnormality. It is therefore reasonably safe to say that these children had normal urological tracts.

The discrepancy between these findings in the apparently normal urological tract and Gruber's findings can be explained by the fact that Gruber's experiments were done on excised bladders. In the excised bladders, only the purely mechanical factor of the ureterovesical valve was present. In the living, viable bladder, it seems reasonable to assume that the factors of muscle contractability and irritability might allow ureteral reflux to occur occasionally in the normal urological tract. Waring pointed out this possibility and cited a case where antiperistalsis occurred and carried a piece of solid material from the bladder into the kidney pelvis.

In this series reflux occurred in 2 cases out of 43, or 4.6 per cent. The true incidence of ureteral reflux might even be higher. As pointed out by Graves, a cystogram cannot be taken as definite evidence that reflux does not exist in any given case. Unless the x-ray caught the opaque substance while it was in the ureter, there would be no evidence of ureteral reflux.

SUMMARY

Forty-three cystograms were done on children who had no signs or symptoms of urinary disease. Two of these children showed ureteral reflux; two others revealed unsuspected bladder diverticula.

This investigation shows that ureteral reflux may occur in children who have apparently normal urological tracts.

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PAPILLARY CARCINOMA OF URETER AND BLADDER ARISING AFTER NEPHRECTOMY FOR TUMOR OF KIDNEY PELVIS[1]

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The purpose of this paper is to emphasize once again the accepted treatment of operable papillary carcinoma of the renal pelvis and to cite a case in point. The group of tumors which arise in the kidney pelvis and calyces is quite different from those arising in the parenchyma and comprises between 5 and 15 per cent of all kidney tumors. Melicow classified them simply as 1) papillary tumors of renal pelvis and 2) nonpapillary tumors of renal pelvis. The papillary tumors may be either "benign" papilloma or malignant papillary carcinoma. The nonpapillary growths tend towards squamous cell metaplasia. Approximately 75 per cent of pelvic tumors fall in the papillary group and about 60 per cent of these are of the malignant variety. Discussion will be limited to this 75 per cent.

The gross and histological picture of both the benign papilloma and papillary carcinoma of the pelvis is the same as for corresponding vesical neoplasms. There is a distinct tendency to grow slowly but continually into the lumen rather than to invade the parenchyma; this latter occurring, however, with increasing malignancy. The more benign growth occurs in the younger group while the infiltrating types occur in the older age group. There is a definite tendency for papillary pelvic tumors to recur in the bladder and ureters. Melicow believes that there may be a neoplastigenic tendency of the entire urothelium (ureter, bladder, urethra). The terms "auto-transplantation" and "seeding" have also been used to describe this phenomenon. Whatever the explanation may be, it is generally agreed that nephro-ureterectomy with removal of a cuff of bladder around the corresponding ureteral orifice, as originally proposed by Walters, offers the only reasonable chance against recurrence of these tumors. The operation may be done in one or two stages, depending on the condition of the patient. Less radical procedures have proven ineffective in the past, as the following case will bear out. Even in the case of the benign papillary growth in the kidney pelvis, there are instances of recurrences in the ureteral stump and bladder at a later date and these recurrences many times are malignant.

CASE REPORT

W. F. M. (R No. 726), a 54 year old white man, was admitted to Lawson Veterans' Administration Hospital on October 14, 1946, complaining of "cramping pain in the lower abdomen." A review of old charts revealed that the patient had been hospitalized from August 29, 1945 to November 20, 1945 at another institution. The patient on admission at that time gave a history of hematuria at intervals since November 1944. He had lost 10–15 pounds in the previous year and also had noticed slight dysuria during the past year. Cystoscopy done at that time revealed no evidence of tumor of the bladder but retrograde pyelograms showed a typical filling defect in the pelvis of the left kidney (fig. 1, A). Left nephrectomy was performed. Pathological report was a malignant papilloma in the left kidney pelvis. Following nephrectomy, the patient had deep x-ray therapy through three portals for a total of 6000 roentgen units.

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One month after discharge from the hospital the patient experienced a cramping pain in the lower abdomen, mainly on the left side, constant in character, being aggravated by standing and relieved somewhat after urination. About 3 months before this admission he had noticed his urine was "dark." His local physician made a diagnosis of prostate trouble and treated the patient by massage. Lately there had been frequency of urination with some burning, also nocturia 2 times. Four days before admission the patient had a cystoscopy done by his local doctor who told him he had a mass where the left ureteral orifice was situated and he was advised to come to the hospital.

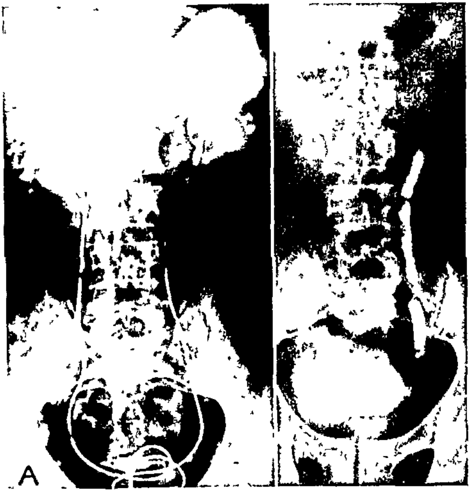

FIG. 1

The remainder of the history was essentially normal except for a chronic spastic colitis which the patient stated began after having bacillary dysentery in the tropics in 1919. There had been no weight loss in the past year.

Temperature, pulse and respiration were normal. The blood pressure was 124/70. The only positive finding was some generalized tenderness to deep pressure over the lower part of the abdomen, particularly on the left side. No masses were palpable. A well healed left nephrectomy scar was present with no evidence of recurrence or herniation. Rectal examination revealed an essentially normal prostate. Urinalysis taken on the present admission reported straw color, acid reaction, specific gravity of 1.015 and 1 plus albumin, 45–50 white blood cells per high power field and an occasional red cell. The nonprotein nitrogen was 36 mg per cent, the hemoglobin 76 per cent. Cystoscopy on October 16 revealed a pedunculated papillary tumor overlying the left ureteral orifice. The left ureteral orifice could not be visualized. The base of the tumor measured approximately 1 by 1½ cm. The biopsy report was infiltrating papillary carcinoma, grade III. On October 21 a transurethral resection of the tumor was done and the base fulgurated. On November 14 cystoscopy revealed an area of approximately 1 by 2 cm. in the region of the left ureteral ledge where the tumor had been previously removed and its base fulgurated. The area at this time was covered with adherent grayish exudate and was surrounded by a great deal of edema. The patient was sent home on a convalescent leave and was again subjected to cystoscopy December 3. At this time it was determined that the majority of the tumor had been removed by electrocoagulation. Extending from the left orifice were numerous small finger-like projections which were diagnosed as tumor. A 5 F catheter was passed by the mass for a distance of 13 cm. and skiodan injected. Ureterograms (fig. 1,*B*) revealed numerous filling defects of the left ureter. A diagnosis was made of papillary carcinoma of the ureter and bladder. The patient received transfusions and was taken to the operating room on January 22 where the ureter and a portion of the bladder around the left ureteral orifice were removed. The ureter was somewhat adherent in the upper portion but there appeared to be no extension of tumorous growth into the periureteral tissue nor involvement of the retroperitoneal nodes. The ureter, when opened, revealed three distinct areas of papillary carcinoma

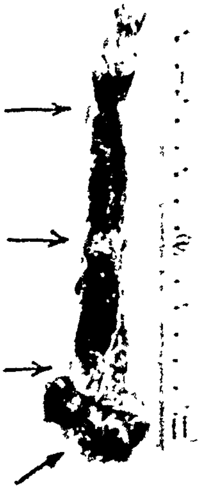

FIG. 2

plus an additional area in the intramural portion of the bladder (fig 2) The patient had an uneventful postoperative recovery The wound healed by primary intention. X-rays of the chest revealed some adhesions in the left costophrenic angle These did not change over a 2 months' period and were not thought to be representative of any pulmonary metastasis X-ray of the long bones and spine were negative for metastasis Pyelograms revealed no involvement of right kidney Cystoscopy showed no evidence of any recurrence of tumor of the bladder at the time of this writing

SUMMARY AND CONCLUSIONS

Tumors arising in the kidney pelvis and calyces comprise between 5 and 15 per cent of all kidney tumors

Approximately 75 per cent of these tumors are of the papillary variety and 60 per cent of these are of the malignant type

Papillary tumors of the kidney pelvis and calyces have a tendency to "spread" along the entire urothelium

It is suggested that nephro ureterectomy with removal of a cuff of bladder around the corresponding ureteral orifice offers the best possible chance to prevent recurrences

A case in point is presented

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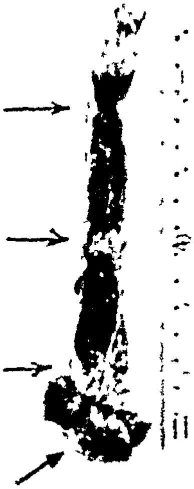

FIG. 2

and hyperglycemia in the etiology of the condition. Of the remaining 32 cases, E. coli were found in 8, while in 24 cases no mention was made of an infectious agent. Diabetes mellitus was present in 6 cases. The sex distribution was equally divided, there being 16 males and 16 females. The oldest case reported was 76; the youngest 12. Only 10 of the patients presented themselves for examination because of genito-urinary complaints, and of these, three were cases of benign prostatic hyperplasia. Of the cases diagnosed antemortem, five recovered and one died. Objective physical findings were not suggestive of the proper diagnosis. Hall reported the presence of crepitation of the abdominal wall over the bladder region. This is not mentioned in other cases and is suggestive of a spreading type of cystitis emphysematosa.

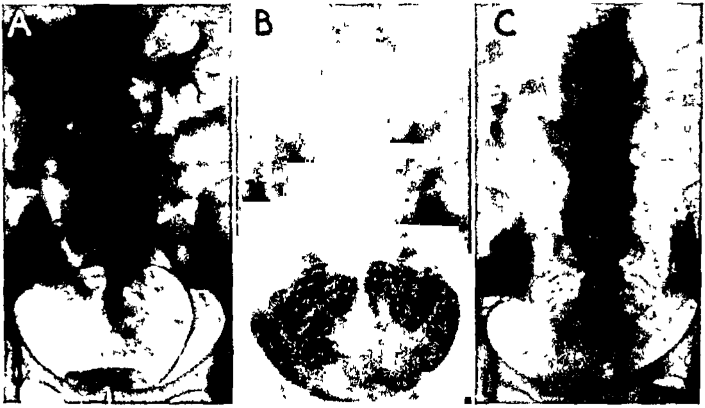

FIG. 1. *A, left retrograde pyelogram, showing normal upper urinary tract. Surrounding* deflated bladder is a ring of air shadows. *B* and *C*, excretory cystogram. With filling of bladder *by opaque fluid from kidneys, ring of air is seen to change its position and shape* with alterations in bladder fluid.

Lund collected gas from the vesicles covering the wall of the bladder and showed that it was carbon dioxide. The source of the gas is not explained. However, the frequent finding of hyperglycemia suggests a changed metabolic activity occurring in the muscle of the bladder itself with accumulation of carbon dioxide beneath the vesical mucosa. Certainly trauma from urologic procedures has not been ruled out as an etiologic factor. However, the absence of instrumentation in the case being reported and no mention of catheterization in many of the previously reported cases certainly leads one to believe that trauma is not a necessary precursor of the disease and perhaps has little or nothing to do with its etiology.

CASE REPORT

Mrs. E. C., a white woman, aged 65, case No. 823, was admitted to Michael Meagher Hospital May 6, 1947. The author was called to see her on May 8, 1947, because of questionable bladder tumor and nonfunctioning left kidney discovered by excretory urogram. Her chief complaint was pain in the left flank, nausea, and vomiting, of recent duration. Due to previous examination for the same complaint a month earlier an excretory urogram had been requested on present admission. The patient was a known diabetic with gangrene affecting the second and third toes of the left foot. She had been told she had "pus on her kidneys" over a period of 2 to 3 years.

The blood pressure was 170/110. A large ventral hernia was present. The heart sounds were distinct but of poor quality. The temperature was 101 F, pulse 110, respiration 20. There was a gangrenous area on the plantar surface of the second and third left toes.

The urine was cloudy, acid in reaction. Specific gravity was 1.013. A trace of albumin was present. There was a precipitation of sugar, graded 3 plus. Tests for diacetic acid and bile were negative. The hemoglobin was 88 per cent. The erythrocyte count was 4,440,000 and the leucocytes numbered 12,500 per cubic millimeter of blood, with a differential count of 87 neutrophils and 13 lymphocytes. The fasting blood sugar determination was 180 mg. per 100 cc. blood.

On a previous admission to the hospital the history and physical findings were practically the same. During that hospital stay she had an irregular type of temperature curve, the highest point being 103 F. She received intravenous fluids, insulin, and penicillin, with administration of morphine for relief of pain. She left the hospital after a short stay. No improvement was noted in the interim between the previous and present admissions.

An excretory urogram revealed numerous small air bubbles in the region of the bladder. As the different films were examined it was noted that these air bubbles changed their position according to the amount of filling present in the bladder (see fig. 1). A presumptive diagnosis of cystitis emphysematosa was made and the patient scheduled for cystoscopy which was easily done under local anesthesia.

Cystoscopic findings were typical of cystitis emphysematosa. There was a moderate bas fond present. The entire vesical mucosa was rough and shaggy looking with areas of cystitis exhibiting a brilliant red appearance. Interspersed among and between these areas were a large number of small, extremely thin-walled vesicles varying in size from less than a millimeter to 5 or 6 mm. in diameter. Although attached to the mucosa, they were easily movable and would rupture with pressure from the instrument, releasing small bubbles of gas which rose to the dome of the bladder. These vesicles were limited to the lower two-thirds of the bladder. Neither ureteral orifice was seen; however, blind catheterization in the region of the left orifice resulted in passage of the catheter to the left kidney pelvis. The catheter drained well.

A left retrograde pyelogram was done which showed no abnormality of that kidney. A cystogram (fig. 1) showed the air bubbles previously described which shifted their position according to the amount of dye present in the bladder.

Specimens of urine collected from the bladder and left kidney showed the presence of many white blood cells A stain revealed many gram negative bacilli. A culture reported later showed this organism to be E coli The ureteral catheter was left indwelling for drainage

Treatment consisted of daily bladder irrigations, sulamyd, tablets 1, 4 times daily, and streptomycin 1 gm every 24 hours

The temperature quickly returned to normal. It was planned to repeat cystoscopy and evaluate the effects of treatment, but the patient left the hospital without her physician's permission and did not return for further examination She died 4 weeks later, apparently in diabetic coma, without being seen again by the author

COMMENTS AND CONCLUSIONS

A case of cystitis emphysematosa is reported This is the forty-fourth case reported in literature available to the author and the seventh case discovered antemortem

An infection by E coli was present as was a hyperglycemia accompanying diabetes mellitus

The importance of a translucent ring of air bubbles in the bladder wall as a diagnostic feature is clearly demonstrated by means of cystograms

The etiology is still obscure, but the role of trauma is questionable The most common findings in the cases reported were hyperglycemia and infection by gas forming organisms

Continued reporting of such cases is important in setting forth criteria for explanation of the pathology

No diagnostic symptoms nor physical findings are described which would lead one to suspect such a diagnosis The first suspicion of such a lesion may follow excretory urography and can be confirmed by cystoscopy or cystostomy

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[1] Arranged in chronological order

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PREGNANCY ASSOCIATED WITH EXSTROPHY OF THE BLADDER

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Exstrophy of the bladder (ectopia vesicae) is a congenital abnormality manifested by the absence of the anterior bladder and anterior lower abdominal walls with eversion of the posterior bladder wall. There always are genital abnormalities accompanying the bladder exstrophy. In the female, there is usually complete absence of the urethra. The clitoris may be cleft or completely absent, with wide separation of the labia, exposing the vaginal orifice. There may be anomalies of the vagina and uterus, i.e., bicornuate uterus and double vagina. There may be complete absence or wide separation of the symphysis pubis.

Congenital bladder exstrophy occurs rarely, about once in 25,000 to 50,000 births. The condition is much more frequent in the male than in the female (5:1).

Until recently, the prognosis for these patients was poor. Over one-half to two-thirds of these patients died before their twentieth year of life due to renal infection and insufficiency resulting from progressive pyelonephritis and pyonephrosis. Today, the outlook is somewhat better due to early surgical intervention with bilateral uretero-intestinal transplantation.

Because of the urinary incontinence and the continual bathing of the genitals with urine, sexual activity is frequently distasteful to both partners. However, in rare instances, pregnancy has occurred with congenital exstrophy of the bladder.

REVIEW OF THE LITERATURE

Randall and Hardwick (1934) reviewed the literature on pregnancy and parturition in females with congenital bladder exstrophy. This review, including 4 cases reported by these authors, revealed that 28 children were born to 20 women who had congenital exstrophy of the bladder. The review did not include a case reported by Dawson (1933). Additional cases were reported by Damm (1937), Schumann (1942), and Ostergaard (1943).

The case reported by Dawson was that of a 27 year old woman on whom repeated bladder plastics had failed. The patient was delivered at term by classical Cesarean section and was sterilized by tubal resection. Recovery was uncomplicated. Damm's case was that of a female who, as long as she could remember, had a uterine prolapse associated with her congenital bladder exstrophy. In childhood she had a transplantation of the ureters to the anterior abdominal wall and removal of the exstrophied bladder. She had a term pregnancy with intrauterine death of the fetus. The fetus was delivered by a vaginal cesarean section, version, and perforation of the aftercoming head. Recovery was uncomplicated. Schumann's patient had surgery prior to pregnancy. A Maydl operation had been performed (transplantation of the ureters and the trigone of the bladder intact to the sigmoid colon with a permanent colostomy)

Ostergaard reported a case of a 39 year old female who had had no previous surgery for the bladder exstrophy and who delivered a live baby vaginally, complicated by a postpartum prolapse

Search of the literature reveals that 33 children have been born to 26 women who had congenital bladder exstrophy, including the case reported here Six of the deliveries were by cesarean section Vaginal delivery was accomplished in 27 cases Eight were stillborn and 25 were born alive Twelve cases gave no history of attempted surgical repair of the bladder exstrophy Fourteen cases gave a history of various types of attempted surgical repair, three of these after the delivery of the child To these cases, the authors wish to add an additional case

CASE REPORT

Mrs S Y , a colored woman, aged 31 years, was first seen in the prenatal clinic of Michael Reese Hospital on August 6, 1946 As long as the patient could remember, her bladder was open on her abdominal wall She had several operations on the bladder at Cook County Hospital when she was 6 years of age The discharge diagnosis obtained from the master card file of this institution was "exstrophy of the bladder " The patient's last normal menstrual period had occurred on May 13, 1946

The patient was admitted to the hospital on the service of Dr Ralph Reis Inventory by systems, family history, and past history were essentially negative except as noted above Blood pressure was 122/78, temperature, pulse and respiration were normal The heart and lungs was normal On examination of the abdomen, the uterus was palpable 8 cm above the pubic area In the suprapubic area there was a wide scar at the base of which was a mass approximately 1 cm in diameter, which resembled granulation tissue The mons veneris, clitoris and urethra were absent The labia majora were widely separated superiorly (fig 1, A) Urine could be seen dribbling intermittently from the above described granular area, which proved to be the exstrophied bladder The umbilicus was absent

On vaginal examination, the introitus was gaping The pubic symphysis was absent and the pubic rami were widely separated but connected by a dense fibrous band The ischial spines were blunt, the sacrum was normal The cervix was smooth and soft and the uterus was enlarged to the size of a 10 to 12 week gestation The internal anteroposterior diameter of the pelvis from the sacral promontory to the fibrous band anteriorly exceeded 13 cm

In spite of the bony fault of the pelvis, the posture and gait of the patient were completely normal (fig 1, *B*) X-ray examination of the pelvis disclosed agenesis of the pubic rami with wide separation of the ischia A fetus of approximately 3½ months' gestation was demonstrable lying in the true pelvis Excretion urography showed bilateral thrust excretion of the dye in 5 minutes with progression in the 15 and 30 minute films These films revealed markedly dilated renal pelves and ureters (fig 2)

Laboratory studies were all within normal range The Kahn test was nega-

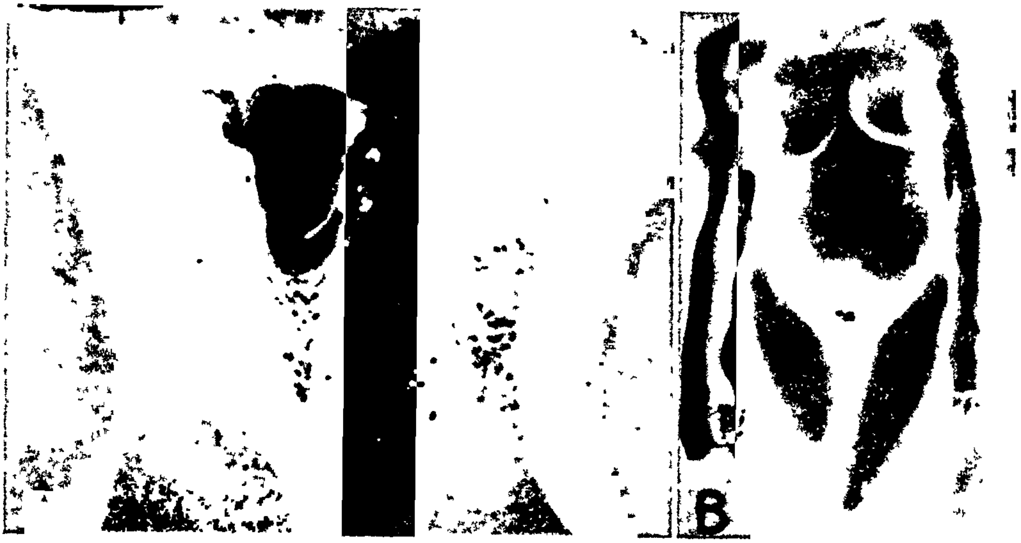

FIG. 1. *A*, photograph, showing scarring from previous efforts at surgical correction; bladder exstrophy; absence of clitoris and wide cleft of labia majora; gaping introitus; deep perineum. *B*, exstrophy of bladder. Pregnancy has progressed to approximately 7 months' duration.

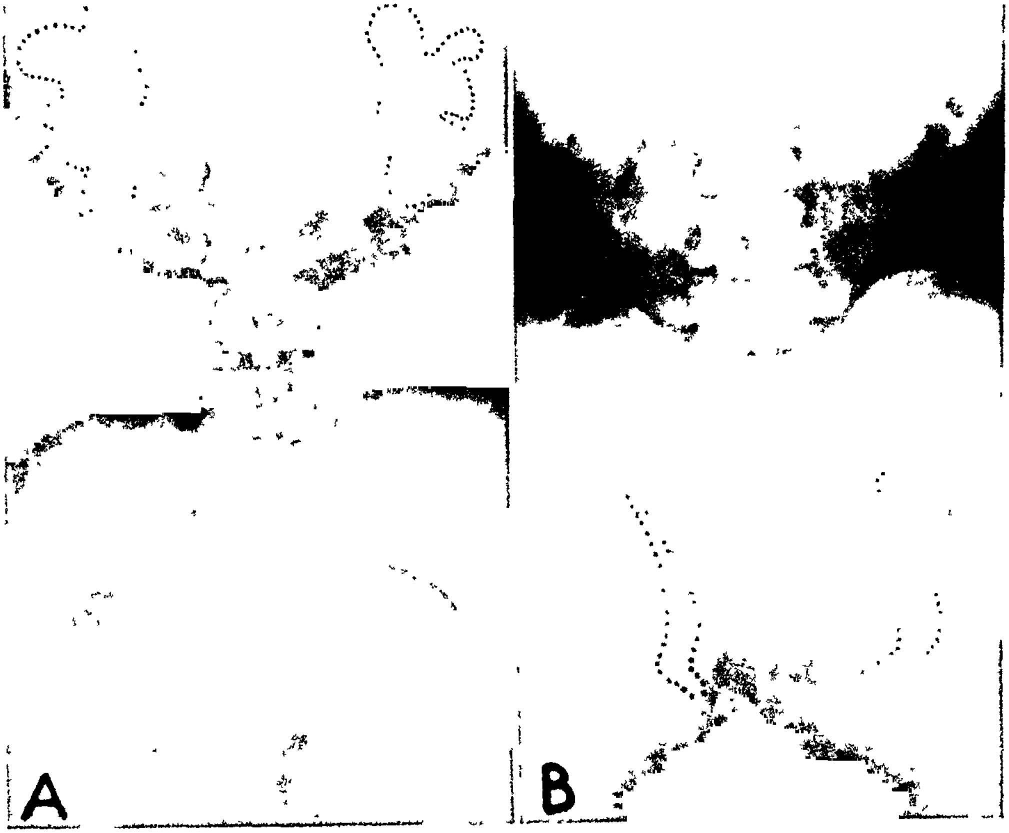

FIG. 2. Excretory urogram, 3½ months' gestation, revealing dilated renal pelves and dilated lower ureters. Note absence of pubic symphysis and wide separation of vestigial pubic rami.

tive; hematologic evaluation was normal. The urine, collected from the exstrophy, showed only a trace of albumin. Blood chemistry (urea nitrogen, blood glucose, creatinine, serum uric acid, total proteins, serum albumin, A/G ratio) was within normal range.

It is of interest to note here that the patient required relatively few pads over the exstrophied bladder to keep dry. She would experience the sensation of a desire to urinate and could accomplish the evacuation of sizeable quantities of urine through the ureteric orifices voluntarily. The patient was dismissed from the hospital and followed in the prenatal clinic.

The patient was readmitted to the hospital on October 7, 1946, for repeat excretion urography. Findings at this time showed no change in the pelvic defect. The pregnancy had advanced to 6 months' duration. There was insufficient concentration of the opaque material during 60 minutes to outline the kidney pelves clearly. Fifteen minute examination showed some opaque material in the left renal pelvis suggesting marked dilatation, but the findings were not inconsistent with those normally demonstrated during pregnancy. Gas and fecal material interfered with demonstration of the right kidney pelvis. Blood chemical studies were repeated prior to discharge from the hospital and were entirely normal.

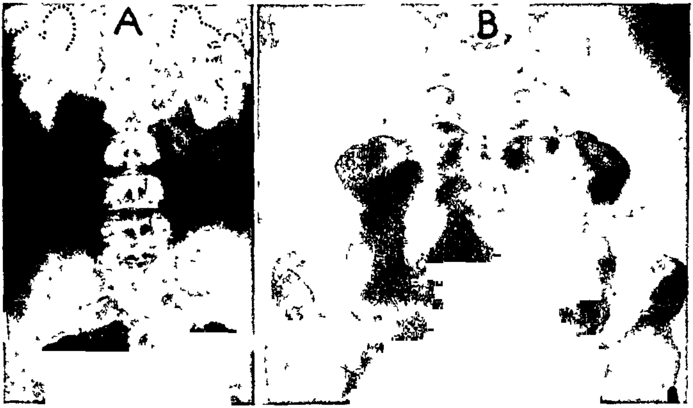

FIG. 3. Excretory urogram, 3 months' postpartum. Marked dilatation of renal pelves and ureters shows no regression

On December 18, 1946, the patient was again admitted to the hospital because of the detection of a blood pressure elevation to 148/82 and a finding of 1 plus albumin in a urine specimen. With bed rest, mild sedation and limitation of salt, the blood pressure came down to 128/80, and urinalysis became negative within 3 days. Repeat blood chemistry determinations remained within normal range and the patient was again discharged.

On February 17, 1947, labor was initiated spontaneously, and progressed rapidly, lasting a total of 6 hours. The position and presentation of the fetus were occiput right posterior with spontaneous rotation to occiput right anterior. When the fetal head crowned, the anterior lip of the cervix was visible outside the introitus over the occiput of the fetal head. With bearing down efforts, two streams of urine spurted into the air, one stream from each ureteric orifice. The perineum was deep, so a median episiotomy was done and outlet forceps used to effect the delivery of a normal male infant weighting seven pounds, five ounces. The third stage of labor was uncomplicated. Palpation of the fibrous tissue symphyseal band revealed it to be intact.

The puerperium was essentially normal and the patient was discharged on the eleventh postpartum day. Follow-up examination 7 weeks after delivery revealed the episiotomy to be well healed and the perineum firm. The uterus was well involuted, in first degree retroversion and movable. The cervix was well epithelialized. The adnexa were not palpable. The patient's gait was normal and the fibrous band intact.

An intravenous pyelogram 3 months postpartum showed immediate thrust excretion of the dye bilaterally with progression through the fifteen and thirty minute examinations. Both renal pelves and ureters were markedly dilated, showing no regression, as compared to the prepartum urograms (fig. 3).

The patient was last seen on July 25, 1947, four and one-half months since delivery. She stated that on occasion "something protruded from the vagina." Examination in dorsal recumbent position revealed no change from the previous examination. However, examination with the patient upright, and after straining, showed that the cervix descended to the introitus.

DISCUSSION

In the review by Dawson, he states that all patients with bladder exstrophy who become pregnant should be delivered by elective cesarean section. The reason given is that this procedure may obviate the development of genital prolapse after delivery. Certainly a large percentage of the reported cases that were delivered from below did develop prolapse of the uterus postpartum. It is of interest to note, however, that there are reported 3 cases of uterine prolapse in nulliparous women with exstrophy of the bladder. One of these patients (Damm) subsequently became pregnant. The other cases are reported by Ismail and Clayton.

For several reasons our patient was allowed to deliver per vaginum. 1) Several attempts at correction of the bladder exstrophy had resulted in extensive scarring of the abdominal wall and the amount of possible anatomic distortion was an unknown factor. 2) The patient would not permit sterilization. Since it was felt that a classical cesarean section was the only type of operation possible, the resultant potential hazard of repeated classical cesarean section in future childbearing warranted the risk of postpartum genital prolapse. This seemed especially true since, in women with bladder exstrophy, prolapse of the uterus may occur even without the trauma incident to childbearing.

Another report found in the literature is of interest. McKenzie describes a patient who had a "split pelvis" but had no bladder exstrophy. For obstetrical indications the patient required a cesarean section and a laparotrachelotomy was performed. The bladder was encountered under the skin of the abdominal wall incorporated into the anterior abdominal fascia. This report, considered with the cases of exstrophy of the bladder, would indicate that this type of embryonic maldevelopment may vary from the mildest form with no apparent disability to the patient, all the way to extensive anomalies incompatible with life.

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the introitus over the occiput of the fetal head. With bearing down efforts, two streams of urine spurted into the air, one stream from each ureteric orifice. The perineum was deep, so a median episiotomy was done and outlet forceps used to effect the delivery of a normal male infant weighting seven pounds, five ounces. The third stage of labor was uncomplicated. Palpation of the fibrous tissue symphyseal band revealed it to be intact.

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Another report found in the literature is of interest. McKenzie describes a patient who had a "split pelvis" but had no bladder exstrophy. For obstetrical indications the patient required a cesarean section and a laparotrachelotomy was performed. The bladder was encountered under the skin of the abdominal wall under stilbestrol therapy. On August 1, 1947, he was admitted to City Hospital, where he died 8 days later. During this period of observation he developed signs of small bowel obstruction. X-rays showed small bowel obstruction and extensive bony metastases. At operation, a Richter hernia containing a loop of obstructed large bowel was found and repaired. The course was progressive and death occurred 2 days later.

The total stilbestrol administered between August 9, 1946 and July 31, 1947 was 4095 mg.

Autopsy (No. 7978): The pertinent findings only are given. The prostate had a large carcinoma and there were extensive bony metastases, metastases to one adrenal and extensive invasion of the soft tissues of the pelvis causing ureteral obstruction and pyelonephritis.

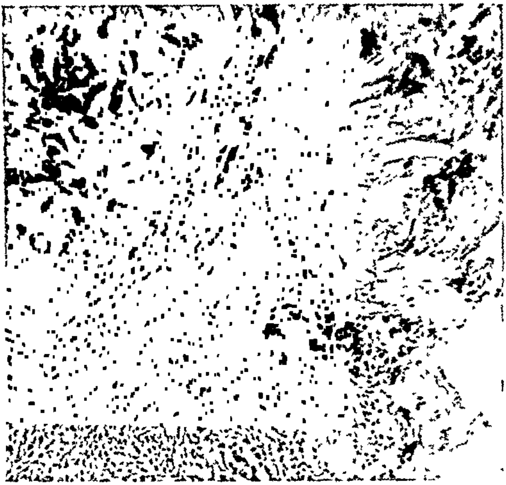

FIG. 1. *Lesion of prostate, showing regression of tumor cells, marked fibrotic response and bone formation.*

The microscopy of the primary tumor showed extensive regressive changes of the neoplasm with marked fibrosis. In some areas the fibrosis had become hyalinized and calcified, resembling bone in its morphological pattern (fig. 1).

COMMENT

The pathogenesis of the formation of bone in prostatic carcinoma is obscure. Huggins in 1931 showed that the epithelium of the urinary bladder has osteogenic properties and suggested the possibility that the same may be true of the prostatic epithelium. Experimental proof was lacking. Histologically the present case resembled Huggins' findings very closely.

The effect of stilbestrol therapy in bone production probably is slight, although definite conclusions cannot be advanced in view of the paucity of data. In the cases of Barringer and Woodward and of Ashburn, stilbesterol was not administered. It is of interest to note, however, that in the present case and in that of Barringer and Woodward, the levels of alkaline serum phosphatase activity were high.

SUMMARY

A case of osteogenesis in a prostatic carcinoma is reported and the literature of this unusual event reviewed.

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FIBROMA OF TUNICA VAGINALIS TESTIS[1]

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Benign tumors of the testicular tunics are still considered rare Their recognition and correct diagnosis are very important, as stressed by Goodwin and Vermooten, especially as to treatment and prognosis The literature has been thoroughly reviewed by the above mentioned authors, who have shown that the classification of these tumors has been somewhat confused They suggested that the term "chronic proliferative periorchitis" be used for simple chronic inflammatory thickening of the testicular tunics, and that "multiple fibromata" be retained for the fibrous nodules that originate in the tunica vaginalis As stated by Thompson it is often very difficult, sometimes practically impossible, to distinguish tumors of the tunica vaginalis from those arising from adjacent structures

A case is presented here which closely resembles the clinical picture described by Goodwin

CASE REPORT

J M , a 50 year old Negro, was admitted to the hospital with the diagnosis of a left testicular tumor This tumor was first noticed 3 years previously, when it was about 1 cm in diameter, and it had gradually increased in size It was painless, and there was no history of trauma or venereal disease The patient later stated that his scrotum had been "tapped" twice about 3 years previously without the removal of any fluid The patient was also a mild diabetic

General examination was essentially negative Examination of the external genitalia revealed a large mass in the left side of the scrotum, measuring about 9 cm in diameter and 12 cm in length It was firm, nontender and movable The left testicle could not be palpated The mass appeared to be one solid structure and seemed to be part of the testicle, and definitely suggested a malignancy of the left testicle There was no inguinal adenopathy and rectal examination was negative

The urine showed 4 plus sugar The blood sugar was 246 mg per 100 cc and the blood Wassermann was negative The Friedman test gave a slightly positive reaction X rays of the chest, lumbo sacral spine and pelvis were normal X ray of the tumor mass revealed no calcifications Intravenous pyelography showed no abnormalities

It was decided that an exploratory operation was indicated, with probable orchidectomy On opening the scrotum, under spinal anesthesia, a large mass measuring 11 by 9 by 9 cm was exposed It was firmly adherent to the tunica vaginalis, so that the testis or epididymis could not be readily exposed Facilities for biopsy at the time of operation were not available It was decided that

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[1] Published with the permission of the Chief Medical Director Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author

SUMMARY

A case of a large fibroma of the tunica vaginalis testis is presented.

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ANORCHISM

ROBERT H HEPBURN

Twelve cases of anorchism have been reported in the literature. A thirteenth case was recently seen at the Hartford Hospital.

CASE REPORT

S W, aged 19, had been medically treated by his physician for several months because of impalpable testes, epididymes, and vasa deferentia. No improvement was noted and the patient was referred to me.

He was in excellent health. He had typical eunuchoid physical characteristics: his hips were large, his shoulders narrow, his muscular development poor. His span was 175 cm, height 170 cm. There was almost no facial, axillary, or pubic hair (fig 1). Careful examination of the inguinal canals and scrotum, perineum and upper thighs failed to reveal any evidence of testes or wolffian structures. No congenital hernias were noted. The penis was 1¼ inches long. The prostate was barely distinguishable, about the size of a dime. It is of interest that though erections had not been infrequent, the penis measuring about 3 inches on these occasions, there had never been orgasm or ejaculation.

Because of the question of abdominal cryptorchidism, exploration was done. The patient's eunuchoid characteristics indicated the possibility of anorchism. Accordingly, abdominal approach was used to permit more satisfactory exposure.

A lower midline abdominal incision was chosen. The right vestigial vas was ⅓ normal diameter, disappearing outward into a tightly closed inguinal canal. No evidence of testes was seen anywhere in this region or cephalad along the lateral abdominal wall. Similar exploration was done with similar results on the left, except for the absence of any vas whatsoever. On this side the posterior peritoneum was opened, retroperitoneal exploration throughout this area revealed no testes or wolffian structures. The bladder was mobilized bilaterally, the large bowel explored, again no evidence of testes or wolffian elements was seen. The appendix was removed. The abdomen was closed in layers. Convalescence was uneventful.

THE LITERATURE

The cases in the literature were reviewed by Counseller and Walker. They added a case of their own. Heller et al observed 2 cases. These are all presented briefly to give the complete picture under one communication.

Observed at necropsy

Cabral	1564	No testes in man hanged for rape
Anonymous Author	1732	Dissected body of youth found dead in street. No testes
Kretschmer	1801	Eight day old infant. Complete absence of testes, cords, vesicles. Complete anal atresia, opening through prostate connected rectum to urethra causing passage of meconium and feces in the urine

Fisher	1839	(First American case.) Patient 45 years old, died of pneumonia. Never had any sex desire. Feminine habitus, little facial or pubic hair. Penis size of 10 year old boy. Small scrotum without testes. Left vas ended in small nodule throught to be epididymis; right vas ended in small vas-like dilatation.
Friese	1841	Full term fetus. No testes or epididymis. Vasa, vesicles, and other organs normal.
Godard	1860	Sixty-one year-old man whose voice and habitus had always been feminine. Never had intercourse. No axillary, facial or pubic hair. Penis 35 mm. long. No scrotum. Empty inguinal canals. No epididymes or testes. Vasa ended blindly in peritoneum behind both inguinal regions. Seminal vesicles present.

Observed at operation

Wildbolz	1917	Twenty year-old man without testes. Never had erections, emissions, libido. Feminine habitus. No axillary, facial, or pubic hair. Penis 4 cm. long. Prostate and vesicles not palpable. Scrotum very small. No hernias. Bilateral inguinal incisions made. Small but complete left cord reaching well into scrotum. Vas 2.15 mm. in diameter ending in rounded mass of connective tissue 10 by 8 by 4 mm. Similar on right, but cord ended at entrance to scrotum and there was no swelling at end of vas. Palpation of abdominal cavity in region of inguinal rings failed to reveal any suggestion of testes. Microscopically the mass at the end of the left vas showed fibrous tissue plus a few atrophic tubules probably remains of an epididymis.
Koopman	1930	Twins, aged 13, feeble-minded. Each had small penis, small empty scrotum, no palpable testes. Shortly afterwards one of boys operated on for acute appendicitis. No trace of testes found in inguinal canals or abdomen. Cord present on both sides but with small vessels ending in skin of scrotum. Prostate present. Seminal vesicles absent.
Counseller and Walker	1932	Boy aged 14. History noncontributory. Well developed and nourished, 62 inches tall, weight 96 pounds, blood pressure 128/78. Infantile penis, small scrotum. Symphysis covered by large pad of fat. At operation no external inguinal ring found. Vas deferens extended throughout the inguinal canal and terminated as an atrophic cord as it neared the pubis. Entire right lower abdominal area explored; no testis found. Similar exploration on left; no genital structures found.
		Boy aged 11. History noncontributory. Three normally developed siblings. Well developed and nourished. Height 5 feet 9 inches, weight 92 pounds. Normal penis

		for his age. No palpable testes. No hernias. Right inguinal exploration; small vas could be palpated ending at about site of internal ring and terminating in a small fatty nodule possibly a rudimentary epididymis. The vas could be palpated as it ran posteriorly beneath peritoneum, but no testis was found. Incision enlarged and same findings noted on left.
Heller et al.	1943	Boy aged 14. Bilateral inguinal incision. Epididymis and vas on left. Vas on right. No testes in canals or adjacent abdomen. Boy aged 19. No wolffian duct structures on left; probable atrophic vas deferens on right. No testes.

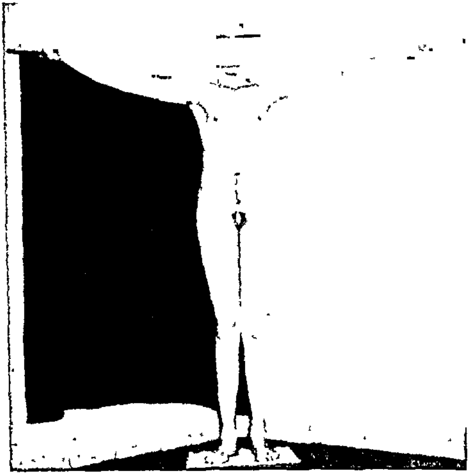

FIG. 1. Eunuchoid characteristics of sparse facial, pubic, and axillary hair, large hips, span greater than height. Small penis, empty scrotum.

COMMENT

The case reported is a normal boy in his social life, likes to take girls out, and competes successfully in his white-collar work at an industrial concern. He takes his deficiency without neurosis and does not require substitution therapy. Assays of pituitary luteinizing and follicle stimulating hormone together with urinary 17-ketosteroids were not available. It would have been of interest to correlate them with personality and physical characteristics. No case of anorchia with absence of or nonincreased F.S.H. or L.H. has yet been reported. Could preexisting over-production or under-production of these pituitary hormones cause anorchia or is this condition primary in some more obscure embryological mishap?

SUMMARY

A thirteenth case of anorchism is reported. The literature is summarized.

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PROGNOSIS OF TESTICULAR TUMORS[1]

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It is apparent that only a large amount of clinical material, followed over a long period of time, can be used as a basis to properly evaluate the significance of certain factors which may have influence on the prognosis of malignant disease. In the comparatively rare testicular tumors it was difficult in the past to collect a sufficient number of patients for analysis; but large series of cases have become available for study during the war, when hundreds of patients with this type of malignancy were admitted to the various hospitals of the Armed Forces. The recent investigations of Lewis, and Friedman and Moore, which were based on this material, are important inasmuch as they have suggested a new approach to this problem and as a result, much interest has been stimulated in this subject during the past few years.

The work of Friedman and Moore has induced us to review and reclassify the material of the Roswell Park Memorial Institute in accordance with the criteria adopted by the Army Institute of Pathology. A series of 202 cases of testicular tumors admitted during a 25 year period (January 1, 1922 to December 31, 1946) was analyzed and an attempt was made to correlate the histo-pathological findings and the clinical course of the disease. In using Friedman and Moore's simplified classifications, the material was grouped as follows:

	Number	*Per cent*
Seminoma	94	(46.9)
Embryonal carcinoma	70	(34.6)
Chorio-carcinoma	3	(1.5)
Terato-carcinoma	27	(13.4)
Adult teratoma	5	(2.5)
Miscellaneous	3	(1.5)
Total	202	(100)

The end results obtained in this case series are herewith presented: 96 patients are alive and well, 2 are alive with the disease, 95 died of the disease, 3 died of other causes and the follow-up in 6 was not complete. This represents an over-all cure rate of 47.5 per cent.

It was concluded that the prognosis in patients with testicular neoplasms depends mainly on 3 factors; namely, histopathology, biological properties and stage of the disease at the beginning of treatment. Also, the method or methods of treatment, if employed adequately, determine in a large measure the ultimate outcome.

Among the factors enumerated, the histopathological characteristics of the tumor must be considered of the greatest importance in the determination of the prognosis in each individual case. Study of the data collected indicated that the outlook improves in direct proportion to the degree of differentiation of a testicular neoplasm. While patients with differentiated or mature cell tumors offer a comparatively fair prognosis, it was found that the prognosis is less favorable if the tumor consists of undifferentiated cells of embryonal origin. It was determined also that the presence of differentiated or adult teratomatous cell structures in an otherwise purely embryonal cell tumor improves the prognosis significantly.

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[1] Abstracts read at 4th International Cancer Congress, September 6, 1947, St. Louis, Mo.

As a result of these observations, the following outline of prognosis is presented: It is best in patients with adult teratoma and almost as good in cases of seminoma. The outlook is less favorable in patients with terato-carcinoma or patients with embryonal carcinoma containing an admixture of seminoma with both of these groups having an approximately equal cure rate. The prognosis is unfavorable in patients with tumors consisting of embryonal carcinoma with or without an admixture of chorio-epithelioma, and least favorable in patients with plain chorio-epithelioma (table 1).

TABLE 1. *Over-all cures in various types of testicular tumors*

	PER CENT
Adult teratoma	80.0
Seminoma with moderate or abundant lymphoid stroma	69.3
Seminoma with little or no lymphoid stroma	42.9
Terato-carcinoma	44.4
Embryonal carcinoma plus seminoma	46.7
Embryonal carcinoma, plain or with other malignant cell structures	22.5

It is realized that the number of our patients with adult teratoma is too small to permit conclusions of accurate value; however, the results in these cases were in agreement with the observations of other investigators. Four, or 80 per cent of 5 patients with adult teratoma survived and 1 patient died of metastatic disease. Whether metastases in this type of neoplasm are due to emboli of complex teratoid tissue plugs or due to differentiation in situ of originally undifferentiated cell constituents is still subject to controversy.

The over-all cure rate in 94 patients with seminoma amounted to 59.6 per cent (56 patients). However, study of the material revealed that the outlook in this type of tumor was seemingly dependent on two main factors, namely, on the patient's age and on the amount of lymphoid stroma encountered in the tumor bed. As to the age factor, it was determined that 83.3 per cent or 5 of 6 patients over 60 years died of the disease. This compares with a mortality rate of only 31.4 per cent or 28 out of 88 patients under 60 years of age. The influence of the amount of lymphoid stroma on the prognosis in patients with seminoma is subject to much controversy. It was determined that the death rate was approximately twice as high (51.4 per cent of 35 cases) in cases of seminoma containing little or no lymphoid stroma as compared to those where a moderate or abundant amount of lymphoid stroma was present (25.4 per cent of 59 cases). It is difficult to find an entirely satisfactory explanation for this phenomenon. Lymphoid stroma does not represent a constituent of the tumor proper, but we are inclined to believe that its presence or absence may serve as an indication as to the rate of growth and as to the degree of aggressiveness of the neoplasm. By way of illustration, it was found that the time interval between onset of symptoms due to testicular tumor and the appearance of demonstrable metastases averaged approximately 8 months for the group of seminomas with little or no lymphoid stroma while it was about 19 months for seminomas with moderate or abundant lymphoid stroma. These observations suggest, in our opinion, that the presence of an appreciable amount of lymphoid stroma in the tumor bed may indicate a defense mechanism which has time to develop in certain types of slow-growing seminomas.

An analysis of the prognosis in patients with embryonal carcinoma is particularly difficult because this term embraces a considerable variety of testicular neoplasms, which, dependent on their constituent cell elements, exhibit different grades of malignancy. It was observed in these types of tumors that the degree of differentiation of tissue of embryonal origin did not influence the course of the disease materially, but it was quite apparent that the presence of teratomatous or seminomatous tissue rendered these tumors less malignant while an admixture of chorionic structures implied a more grave prognosis. If such a mixed tumor was composed of a variety of cell elements of different degrees of malignancy, it was apparent that the most malignant constituents of the neoplasm determined the ultimate outcome.

The following figures serve as an illustration. The over-all cure rate for patients with terato carcinoma and patients with embryonal carcinoma containing an admixture of seminoma was almost equal, namely, 44 per cent and 46.7 per cent respectively. In contrast, a cure rate of only 22.5 per cent was determined for the group of patients with either plain embryonal carcinoma or embryonal carcinoma containing some chorio carcinomatous tissue.

The extremely poor prognosis of patients with chorio epitheliomas is a well-known fact which does not warrant further discussion. The number of these tumors in our group of cases was too small to be of significance.

The aforementioned considerations with regard to relationship between histopathological findings and prognosis indicate clearly that an accurate histological diagnosis in a case of testicular tumor cannot be rendered if only a few selected pieces of tissue are available for study. Serial sections through the entire tumor, and if possible, through metastatic lesions, are essential in order to obtain the greatest degree of accuracy because the presence of certain cell elements in a high or lower grade malignant tumor may have remarkable influence on the clinical course of the disease, and its response to therapy. It ensues that orchidectomy should be carried out in patients with demonstrable metastases also for the purpose of securing adequate material for determination of the prognosis.

In addition to the histopathological characteristics of a testicular neoplasm, certain biological properties of the tumor may assist in evaluating the prognosis. These properties include hormonal activity, rate of growth and degree of radiosensitivity of the tumor.

The value of the Aschheim-Zondek test as a means in determining the prognosis of testicular tumors has been subject to controversy for a number of years. In the past, attempts have been made to correlate the prognosis with the hormone level in the urine. However, this procedure did not withstand critical analysis and the evaluation of this test in patients with testicular tumors has undergone certain changes. It is the present consensus that a diagnostic positive test, based on a complete analysis of the hormonal contents of a 24 hour sample of urine, indicates a grave prognosis while a negative result is of little prognostic significance. Aschheim-Zondek tests were carried out routinely during the past 10 years and the results at the Roswell Park Memorial Institute are in general agreement with the aforementioned statement. Experiences with this test also confirmed Nash and Leddy's observations, that a postive Aschheim-Zondek test usually turns negative following a course of deep x-ray therapy, although the disease continues to progress. In contrast, it was never noticed that an originally negative Aschheim-Zondek reaction became positive during the further course of the disease.

As to the significance of the rate of growth of testicular tumors, it has been noted that the outlook is especially poor in the so-called "hurricane type" of tumor, which terminated fatally almost always within a short period of time, regardless of histology, time of diagnosis or methods of treatment. Also, in tumors with less spectacular tendency to spread, it was found that the rate of growth is of prognostic significance. By way of illustration, in 88 patients who died of the disease, the time interval between onset of symptoms and diagnosis averaged 8 months, as compared to 12.8 months in 89 patients who survived. These figures indicate that rapid progression of the disease should be viewed as a bad prognostic sign, while a slow-growing testicular tumor indicates a more favorable outlook.

The degree of radiosensitivity of a testicular neoplasm represents another valuable adjunct in determining the prognosis. Since preoperative radiation of the primary lesion has been generally abandoned, the radio-sensitivity of a tumor is evaluated best by the study of the response of metastases to radiation therapy. It is well known that various types of testicular tumors require different amounts of radiation energy for their destruction. For example, seminomas are often curable by the use of comparatively small doses of x-ray, while the majority of the other types of tumors require, for their destruction, an amount of radiation energy which exceeds the tolerance of healthy tissue.

Following analysis of the material, it became apparent that the initial response of metastatic lesions to radiation therapy represented the most significant prognostic sign. For the purpose of correlating prognosis and radio-responsiveness of a testicular tumor, the cases were grouped as follows: 1) rapid and complete disappearance of metastatic foci after the use of comparatively small doses; 2) complete disappearance of some metastases by the use of small doses and persistence or temporary regression of others following massive doses; 3) complete temporary disappearance or marked temporary regression of metastases in response to large doses; 4) radiation ineffective.

The preceding outline indicates, in a large measure, a definite pattern of prognosis: Favorable end results should be anticipated only in the first group of cases where all metastases consist uniformly of radio sensitive or radio responsive cell elements It was determined that this was the case almost entirely in patients with seminoma (27 7 per cent cures in 47 metastatic cases), or those with embryonal carcinoma plus seminoma (9 8 per cent cures in 51 cases) If only marked regression or disappearance of all but one metastatic lesion is accomplished, the outlook is unfavorable because the effectiveness of radiation therapy remains confined to that part of the tumor which is comprised of radio-sensitive cells Resurgent spread of the disease in these cases results from the surviving radio-resistant cells, which explains that a subsequent course of deep x-ray therapy will be even less effective The same consideration applies also for those patients who develop metastases following an initial course of prophylactic deep x-ray therapy (Nesbit and Lynn)

In addition to the histopathological characteristics and biological properties of testicular neoplasms, the outlook in each case depends, to a large extent, upon the stage of the disease at the beginning of treatment The advantage of an early diagnosis is obvious and need not be discussed, however, in metastatic cases, cure can be accomplished only if metastases can be removed by surgery or destroyed by radiation In both instances, success or failure is determined not only by the type of tumor but also by the stage of the disease While surgical procedures have their limitations in the inaccessibility of metastatic lesions, it must be kept in mind that radiation therapy cannot accomplish cure in cases of advanced carcinomatosis even if the metastases are radio sensitive Study of our data revealed that favorable end results were obtained by the use of deep x-ray therapy only in those patients in whom radio responsive metastases were confined to one or two areas In cases of widespread, though obviously radio-sensitive metastases, radiation could not alter the ultimate outcome, although an appreciable degree of palliation was often obtained

The apparent significance of certain clinical signs and symptoms in regard to prognosis was impressive For instance, persistent or recurrent backache during any stage of the disease should be regarded as a grave prognostic sign even in apparently healthy looking patients It was observed that backache was often an early symptom of metastases, although no objective evidence of metastatic spread of the disease was demonstrable clinically or roentgenologically at this stage of the disease Another sign which seems to indicate a hopeless prognosis was encountered in a number of patients with apparently widespread, but at times, not yet demonstrable metastases These patients complain of excruciating backache and in order to obtain some relief, they lie in bed or sit up with their knees and thighs in an exaggerated flexed position Regardless of treatment, all of these cases terminated fatally within a short period of time, and in several instances, autopsy revealed pressure on nerve roots due to metastatic disease

In conclusion, the following data are presented in regard to the remote prognosis in patients who appear to be free of the disease following treatment The over all cure rate in our series was 47 5 per cent (96 of 202 patients), the 5 year cure rate was 48.9 per cent (70 of 143 patients admitted before December 31, 1941) and the 10 year cure rate was 34.7 per cent (35 of 101 patients admitted before December 31, 1936).

It was determined further that regardless of the type of tumor, death of the disease occurred most often during the first 2 years after onset of symptoms. The mortality rate for this period was 68.4 per cent (65 of 95 patients with an approximately equal number of deaths occurring during the first (35 cases) and second year (30 cases). Hence, the death rate showed a precipitous decrease to approximately 10 per cent for each of the following 3 years (9.4 per cent during third and fourth year, 10.4 per cent during the fifth year). Only 3 patients who survived the 5 year period died of the disease 6, 7 and 11 years respectively. It ensues that any study based on a 2 year follow-up is subject to over 30 per cent error, while any study based on a 5 year follow-up is subject to only 3 per cent error. Accordingly, one is justified in concluding that any 5 year survival without disease is especially significant in cases of testicular tumor because a patient who lives 5 years or more can be considered fairly safe from the possibility of recurrent disease.

SUMMARY

A consideration of the factors which are considered important in regard to prognosis in patients with testicular tumors is presented.

An analysis of 202 testicular tumors observed during a 25 year period indicates that the prognosis depends mainly on 3 factors; namely, histopathology, biological properties and stage of the disease at the initiation of therapy.

The correlation of histopathological characteristics and prognosis revealed that the outlook in general improves in direct proportion to the degree of differentiation of a testicular neoplasm.

Hormonal activity, rate of growth and degree of radio-sensitivity of a testicular neoplasm represent biological properties which may assist in evaluating the prognosis.

The significance of 2, 3, 4 and 5 year survivals is discussed and it is concluded that any patient living 5 years or more can be considered fairly safe from the possibility of recurrent disease.

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VULVAR FUSION

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It is the purpose of this paper to present a study of 110 cases of vulvar fusion which we have seen within the last 14 years and to give a brief résumé of the subject

Vulvar fusion may be defined as an acquired post-inflammatory cohesion of the labia minora In the literature this condition has acquired a varied nomenclature and has been variously described as vulvar fusion, atresia of the vulva, synechia of the vulva, and occlusion of the vestibule Several other related terms have also been used

In 1936, under the title "Atresia of the Vulva," the senior authors presented 8 cases as the first detailed report of this condition in the American literature In a subsequent report Campbell used the term vulvar fusion Since that time we have also adopted this nomenclature as we regard this term as being more descriptive of the actual disease

Considering the frequent incidence of vulvar fusion in both urological and pediatric practices the American literature has been rather scant on this subject Relatively few cases have been reported One of us (P N) in 1934, described the first case in a child 25 months of age, and in 1936, the senior authors reported 8 cases in detail Meredith Campbell, in 1940, presented a comprehensive report on 9 cases of vulvar fusion, 7 of which were noted in the first 2 years of life The eldest patient was 8 years of age Bowles and Childs, in 1943, gave a detailed summary of 20 cases Taylor, in 1941, reported 2 cases with urological symptoms, one of which was in a 74 year old, the other being in a child 7 years of age To date, in the American literature, we have found reports on 29 cases

The foreign literature is extensive R Lederer, in 1929, reported a case in a child 2 years of age In 1930, Vakar reported 15 cases of this type seen in one year, the ages ranging from 2 months to 2½ years In 1934, H Schlack reported 6 cases Cases persisting into adult life have been reported by J B Hellier in 1914 and Margaret Salmond in 1930 Among other authors have been K D Ochsenius, A Scontrino, and E Flusser

ETIOLOGY

We believe that vulvar fusion represents an acquired clinical condition rather than a congenital anomaly We are substantiated in this belief by several facts

In our series of 110 cases, 57 had vaginal examinations at birth and no vulvar fusion was noted in any of these (table 1) Bowles and Childs, in their series, noted that 15 out of 20 cases acquired the condition after birth One case, however, was noted to have fused labia minora at birth This case is the only one we have been able to find in the literature that would support the theory that vulvar fusion is congenital in origin We believe that this case could well represent the end result of a vulvitis that occurred in utero

In 20 per cent of our cases (table 1) there have been one or more recurrences after operative treatment. These recurrences presented the actual clinical appearance of the original vulvar fusion.

Campbell has postulated an embryological background for this cohesion of the labia minora and believes that the rational explanation is that of an embryological midline fusion of the labioscrotal folds on each side similar to that which the two scrotal folds undergo in the male. We can see no adequate embryological explanation which can account for fusion of the labia minora. In the development of the female genitalia each of the labia minora is developed from a genital fold. These genital folds are developed from the lips of a groove on the extremity of the genital tubercle, a structure which appears approximately in the fifth week of life. Since at no time during development is there fusion of the genital folds, it seems improbable that vulvar fusion is due to any inhibition of normal developments in the embryo, as is the case in atresia of the vagina. Furthermore, in our series, we have noted no associated anomalies elsewhere in the body.

TABLE 1. *110 cases of vulvar fusion*

	CASES	PER CENT
Urinary symptoms	22	20.0
Perforations		
Anterior (only)	58	52.7
Multiple	52	47.3
Vaginal examination at birth	57	51.8
Recurrences	23	20.0

Taylor considered the fusion to be congenital in 1 case, but notes in his case report the history of a "picket fence" trauma. In none of our cases has there been any history of previous trauma, nor has there been any history suggesting gonococcal infection or any frank nonspecific vulvitis. Vulvitis was present in only 1 case. Due to the richness in cellularity of the labia minora in young girls and due to the fact that the labia minora lie in close apposition in early life, particularly in the posterior portion, a mild inflammation could easily result in an agglutination of these structures without any marked signs of vulvitis. This view is substantiated by the fact that the posterior portion of the fusing membrane is generally always noted to be the more resistant to separation.

Vakar, in his series, believes that a vulvitis or a vulvo-vaginitis antedated the fusion. Vulvitis was present in 47 per cent of his cases. In his opinion the physiologic desquamative vulvovaginitis of the new born plays an important role. This physiological inflammation serves as a predisposing factor for the penetration of pathogens which in turn is followed by infection and adhesions.

The fragile nature of the cohesion and the ease with which it is separated also bear out the contention that vulvar fusion is an end result of a mild inflammatory process.

SYMPTOMATOLOGY

The subjective symptoms fall into two separate groups. In 80 per cent of this series there were no symptoms referable to the fusion. In this group the diagnosis was made either on routine physical examination or by pelvic examination made at the mother's request.

Urinary symptoms were noted in 20 per cent of the cases. In all of this group tenesmus and frequency of urination were present. In 1 case chronic pyelocystitis of 9 months' duration was apparently due to this form of obstruction. Residual urine both in the vagina and in the bladder was noted in a few instances. Deviation of the urinary stream, pyuria, and straining on urination were of common occurrence. No tendency to pruritis nor masturbation has been noted by us.

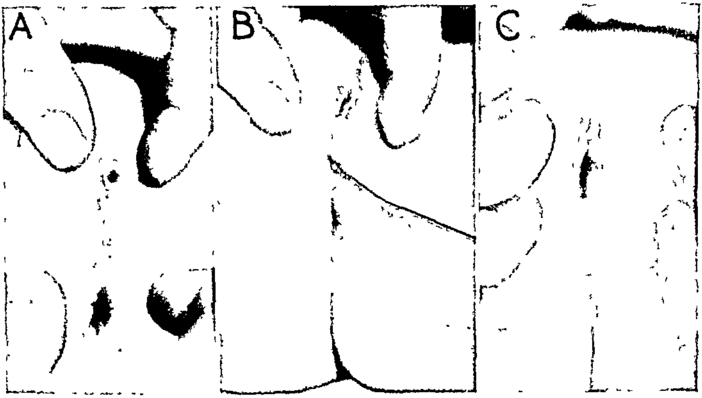

Fig. 1. *A*, vulvar fusion. Note single anterior opening above urethra. *B*, separation of fusion by blunt dissection. A probe has been forced through posterior portion of fusion and passed through anterior aperture seen in *A*. *C*, 3 weeks after separation of fusion.

In this series the youngest was 6½ weeks, the oldest 7½ years.

DIAGNOSIS

On vaginal examination the condition is easily recognized by simple inspection. At first glance one may get the impression that there is some bizarre type of pseudohermaphroditism present, as nothing is seen between the anus and the symphysis pubis but the anterior aperture of the fusion (fig. 1). On separating the labia majora, the labia minora are seen to be sealed together by a thin bluish semi-transparent membrane. This membrane bulges perceptibly during urination. Anteriorly there is a small pinpoint opening just below the clitoris through which the urine emerges. This opening is posterior to the clitoris but well anterior to the urethral meatus, so that in effect there is a diaphragm which tends to obstruct efficient emptying of the bladder.

Fifty-three percent of these cases had only the anterior aperture as described above. In the remaining 47 per cent two to three additional perforations were noted in the midportion of the membrane (table 1). It is our impression that the latter type is less apt to exhibit urinary symptoms.

We have seen no cases in adults, but it is obvious that hematocolpos, and other pelvic manifestations might well follow vulvar fusion if the condition is not recognized and treated early in childhood. Unfortunately no studies of the bladder or upper urinary tract have been made on any of these cases, though they have been frequently advised. The fusion is so easily remedied and the symptoms disappear so quickly that hospitalization for complete urological study has not been carried out. All of these cases have been seen as out-patients.

The following report illustrates some of the problems encountered in a typical case of vulvar fusion.

CASE REPORT

B. G., aged 2½ years, was seen at the Nalle Clinic with the history of repeated attacks of pyelitis over a period of 9 months. These attacks were characterized by elevation of temperature, vomiting, abdominal pain, and marked frequency of urination. Her urine had been examined frequently and was always found to be loaded with pus. Varied medication had been given without benefit. The patient had lost weight, had a poor appetite, and was extremely irritable.

Physical examination revealed a thin, active child not acutely ill. She weighed 25 pounds. The rectal temperature was 99.4 F. Positive findings were limited to the genitalia. When the labia majora were separated, the labia minora were found to be adherent throughout except for a small pinpoint opening just posterior to the clitoris. No urethral orifice could be seen. Traction of the labia produced the appearance of a thin, semitransparent membrane completely occluding the introitus. See figure 1.

During the examination a small amount of urine was passed (with obvious effort). During micturition the fused labia minora were seen to bulge perceptibly, the vagina filling with urine which overflowed through the anterior aperture described above.

The fusion was separated digitally without anesthesia, and boric acid ointment was applied to the denuded surfaces. A 10 F catheter was passed through a normal urethral orifice and 80 cc of cloudy purulent urine were obtained.

All symptoms promptly disappeared, and no recurrence was noted during 2 years of observation. See fiigure 1.

TREATMENT

The treatment consists of simple separation of the labia minora. This may be accomplished by lateral traction manually or by blunt dissection (*fig.* 1, *B*). A bland ointment is used to prevent further agglutination of the raw surfaces. The mother is instructed to inspect the vulva daily and to separate any minute adhesions that may appear.

Anesthesia was necessary in only 4 cases of this series. All of these were over 4 years of age.

One or more recurrences were noted in 20 per cent of our cases, and as Bowles and Childs have noted, *constant vigilance is necessary to prevent further* synechia.

CONCLUSIONS

One hundred and ten cases of vulvar fusion have been observed.

The condition is acquired and is not a congenital anomaly.

The condition may be asymptomatic or may produce symptoms of urinary tract obstruction.

Treatment consists of separation of the labia minora, either manually or by blunt dissection.

Recurrences were noted in 20 per cent of this series.

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HEREDITARY HEMORRHAGIC TELANGIECTASIA AS A CAUSE OF HEMATURIA: TWO CASE REPORTS

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Hereditary hemorrhagic telangiectasia is a well-established disease entity, but the literature, and particularly the urological literature, has been delinquent in listing it as a cause of hematuria; in fact it has been stated that the profession at large seems hardly aware of the existence of the disease.[1] With the proper diagnosis it may account for an appreciable percentage of the cases of so-called "essential hematuria." Although many hundred cases of familial epistaxis, gastro-intestinal and cutaneous bleeding have been reported, less than 30 cases of hereditary hemorrhagic telangiectasia with hematuria have been published.

HISTORICAL

The first recorded observation of familial bleeding other than hemophilia was made by Babington[2] in 1865, who reported a family in which recurrent epistaxis occurred for five generations. No telangiectatic areas were noted, however, in this series. It was not until the turn of the century that the Rendu[3]-Osler[4, 5, 6] - Weber[7] syndrome became established as a disease entity and was termed "multiple heriditary telangiectasia" by Osler. Various names have been applied to designate the condition but until now the standard nomenclature lists the disease as hereditary hemorrhagic telangiectasia. In 1931, Goldstein[8] after a careful search of the world's literature, reported that there were on record 90 to 95 families involving some 500 to 550 persons afflicted with this condition. Hurst,[9] et al. collected reports of 49 other families showing hereditary telangiectasia and added seven families from their own series. Barrock[10] reviewed the literature in 1944.

Guthrie[11] in 1902 reported 12 cases of idiopathic hematuria in one family of 15. Osler[5] in 1907 presented an additional case which was admitted to the Johns Hopkins Hospital for gross hematuria. Aitken[12] in 1902 reported 10 certain and one doubtful case of hematuria in one family. No mention of telangiectasia is made in this report. Pearson[13] reported a man with hematuria due to a hemorrhagic diathesis with familial history of bleeding Mayou[14] reported a patient with multiple telangiectasia of the bladder with intermittent profuse hematuria This individual also had associated telangiectatic areas of the leg Wefeld[15] presented a woman who had profuse hematuria following sexual intercourse Examination of the bladder revealed it to be studded with telangiectasia, angiomata and varices Foggie[16] reported a patient with nasal telangiectasia who had occasional epistaxis and recurring painless hematuria with no other positive urological findings Twelve members of this family had bleeding from telangiectatic areas for five generations No other individual in this family had hematuria.

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Bobbitt,[17] et al. recently reported a case of hematuria for which nephrectomy was performed The pathological description as well as the photomicrographs are suggestive of hereditary hemorrhagic telangiectasia, but no mention is made of telangiectatic areas or history of familial bleeding Many cases of renal hematuria have been reported from angiomas and other tumors of the kidney and renal pelvis These neoplastic processes should not be confused with hereditary hemorrhagic telangiectasia.

PATHOLOGY

Hereditary hemorrhagic telangiectasia is a definite clinical entity, characterized by typical localized dilation of small vessels to form angiomatous lesions with a tendency to bleed from these areas [18] There is no proliferation of vascular elements—the disease is not neoplastic It is a hereditary disease, transmitted by both sexes and occurring equally in both sexes Fitz-Hugh[19] pointed out that the disease may skip one or more generations

The visible local lesions have been described by Steiner[20] as existing in three forms: "the pinpoint, which is most apt to be seen on the skin of the hands and face and which may be readily overlooked, the spider form, which is most common and which Parkes Weber prefers to call spider angiomas rather than spider nevi, the nodular type, which may originate in the center of a spider angioma and finally form a solid vascular tumor, split pea in size They are most frequently seen on the nasal and buccal mucosa and on the mucocutaneous junction of the lips, but may be found in other locations the spots on the mucous membranes always remain a bright red" Those of the skin may be a bluish color In one patient who came under the observation of the author there was marked dilatation of the sublingual blood vessels (fig 1).

Schuster,[21] in a review of the nine autopsies performed on patients with the disease, reported telangiectatic lesions of the skin, nose, mouth, pharynx, larynx, trachea, stomach and duodenum None were present in the kidneys He presented photomicrographs of telangiectatic areas from the skin showing dilated capillaries without inflammation. In another of these cases there were multiple aneurysms of the splenic artery, each about the size of a hazelnut. Osler's[6] only case that came to autopsy did not show renal lesions.

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Little has been written of the microscopic picture of the lesions of familial telangiectasia. Moore[22] states that large sinusoidal spaces appear just beneath the epidermis. Singer and Wolfson[23] classify the disease as one of the hereditary disorders of the capillary structure and function. They state that the characteristic lesions are composed of dilated small vessels that histologically comprise a single layer of endothelium with a conspicuous deficiency of the muscle and elastic layers of the vessel wall. The bleeding from the telangiectatic area is prolonged because of abnormal contractility response. They reported a family with hereditary hemorrhagic telangiectasia with positive tourniquet tests and surmised that it could be present with capillary fragility. Wells[15] also reported 5 cases with positive tourniquet tests, supporting the theory that it may be fundamentally a disease of capillary fragility. This is a new concept of the disease and may eventually alter the diagnostic criteria.

Fig. 1. Case 1. Showing marked dilatation of sublingual vessels

The characteristic lesions do not usually appear until adult life and may go unnoticed by the patient. Nasal and buccal telangiectases are by far the most common and as a result epistaxis and bleeding from the buccal mucosa are the most frequent types of hemorrhages. They occur in the mucous lining of the esophagus, stomach and intestines, giving rise to bleeding from these points. In fact, they have been reported to occur in almost all mucosal lined cavities. Skin lesions are common and frequently give rise to persistent and profuse bleeding. Trauma seems to play an important part in the actuation of hemorrhage.

DIAGNOSIS

The diagnostic criteria were established by Goldstein[5] and confirmed by Larrabe and Littman.[1] They are: 1) definite hereditary tendency, 2) visible typical telangiectatic areas with tendency to bleed from these areas, 3) normal bleeding time, normal clotting time, normal clot retraction time, normal platelet count and negative tourniquet test The condition must be differentiated from hemophilia, pseudohemophilia and the purpuric diseases[18] The blood picture may be altered by prolonged hemorrhage

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Symptoms depend on the location of the lesion and whether or not it is bleeding In the presence of the other diagnostic criteria, hematuria with normal pyelograms and no history of calculi or other urological disease is highly suggestive of renal telangiectasia

TREATMENT

In general, treatment has been unsatisfactory Probably one of the best axioms is to treat only those lesions which bleed, leaving the others alone Cauterization of the offensive areas is the accepted method of handling the accessible lesions Surgical excision of the area or removal of a viscus may, at times, be necessary to control hemorrhage Radiation therapy has been recommended, but has not not met with general acceptance The administration of large doses of iron and general supportive measures to combat anemia are of course indicated Repeated blood transfusions have been necessary in many cases Rutin may prove of value in treating the disease if it is one of capillary fragility as has been suggested.

CASE REPORTS

Case 1 Mrs L P S , a 39 year old cotton mill worker, was admitted to Grady Memorial Hospital on September 9, 1946, with a pain in her left side and bloody urine as her chief complaint The patient dated the onset of her present illness from her second pregnancy 4 years prior to admission At that time she developed a slight pain in the left flank which persisted until delivery It recurred during her third pregnancy and persisted constantly since then, becoming more severe during the past 3 months It was during this third pregnancy that she first noticed that her urine was blood-tinged This hematuria, accompanied by nausea and vomiting, persisted intermittently since the onset and at times became quite severe Three months prior to admission she occasionally passed "stringy blood clots" These symptoms persisted with gradually increasing pain in the left flank and costovertebral angle She gave no history of passing urinary calculi There had been no episodes of epistaxis or bleeding from any other part of her body

Three weeks prior to this admission she was admitted to the gynecological service of Grady Memorial Hospital for repair of a cystocele and rectocele The hematuria was noted and a urological consultation requested Cystoscopic examination at that time showed marked gross hematuria from the left ureteral orifice and blood-tinged urine spurting from the right orifice Retrograde and intravenous pyelograms were normal A second cystoscopic examination done 3 days later confirmed the bleeding from the left upper urinary tract, no bleeding was noted on the right side Examination of the urine sediment for tubercle bacillus was negative Operation for repair of cystocele and rectocele was deferred and she was discharged from the gynecological service with a diagnosis of hematuria, cause undetermined. She was readmitted on September 9, 1946, to the urological service.

There was no family history of tuberculosis or renal calculi. Her mother, who is living and well, had had recurrent epistaxis "all her life." Her maternal grandmother also had many nosebleeds. No other members of her family had abnormal bleeding.

The temperature was normal; respiration, 24; pulse, 76; blood pressure, 122/80. On the anterior portion of the ventral surface of her tongue there were dilated blood vessels, reddish blue in color, which had the appearance of submucous hemorrhages. Posteriorly on the ventral surface of her tongue there were multiple bright red, spider-like telangiectases. There was a reddish-blue spot on her right cheek approximately .5 cm. in diameter which blanched on pressure. The blood vessels of the uvula were also dilated. There were no other telangiectases visible on her body. Heart and lungs were normal. The left side of her abdomen was very tender to palpation and there was marked left costovertebral angle tenderness. The spleen was palpable two to three fingerbreadths below the left costal margin and was soft and tender. The inferior border of the liver was palpable two fingerbreadths below the costal margin and was also tender. The remainder of the physical examination was essentially negative.

The urine was grossly bloody on repeated examinations. There was a trace to 1 plus albumin with 0–10 pus cells in each high power field with occasional clumping in an unspun, catheterized specimen. The urine was negative for sugar. Culture of kidney urine specimens showed no growth from the right and Alkaligenes faecalis from the left. Examination of repeated smears of the urine showed no acid fast organisms. Urine culture for tubercle bacilli was also negative. The red blood count was 3,800,000; hemoglobin 8.1 gm.; platelets 470,000; white blood count 6,250 with a normal differential count. Sedimentation rate was 37 mm. in one hour; hematocrit 31. Coagulation time, 5 min.; prothrombin time, normal; clot retraction time, normal; bleeding time, 2 min.; red blood cell fragility, normal; tourniquet test, negative in each arm. Liver function tests were within normal limits. X-ray of chest was negative.

Cystoscopic examination 4 days after readmission again showed blood coming from the left ureteral orifice, and retrograde and intravenous pyelograms made at this time were normal.

All available members of her family were examined. Her mother showed almost identical lesions of the tongue; there were none on her uvula. In addition, the mother showed spider-like telangiectases of the nasal mucosa.

She was placed on iron therapy. During her 1-day course in the hospital the patient had two episodes of left ureteral colic associated with nausea and vomiting. Her temperature remained normal. The hematuria subsided remarkably and on discharge her urine showed only 20–25 red blood cells per high power field in an unspun, catheterized specimen. Her condition was explained to her and she was told to come back at intervals for check-up.

She has had two attacks of hematuria lasting 4 to 6 days since discharge. The erythrocyte count remains between 4 and 5 million and hemoglobin has remained between 10 and 12 gm Bed rest for several days alleviates the hematuria and associated pain She has been able to resume her work on a part-time basis

Case 2 W T, a 24 year old Negro laborer, was admitted to the urological service of Grady Memorial Hospital on December 11, 1947, with chief complaint of passing blood in urine This was his third admission for hematuria. He dated the onset of his present illness from 3 years prior to this admission At that time he had a period of gross hematuria which lasted approximately 4 months and stopped spontaneously without medication His next episode occurred some 6 months later After passing bloody urine for 2 weeks he came to the outpatient urological clinic and was admitted to the hospital He was profoundly anemic Cystoscopic examination showed bleeding from the left kidney Retrograde pyelograms showed slight hydronephrosis of the left kidney and a drop of 1 cm in the upright position He was given repeated blood transfusions A pyeloplasty and Deming nephropexy were done in April 1945 It is presumed that a diagnosis of chronic pyelonephritis with ureteropelvic obstruction was the basis of this procedure The hematuria subsided for 18 months when he again noted blood in his urine He consulted a private physician and was given medicine which "helped some" This attack lasted only 2 weeks On November 10, 1947, he was again readmitted because of hematuria which had been present for 2 months He complained of fatigue, dyspnea, palpitation and pain in the left flank and costovertebral angle Repeated cystoscopic examinations showed the blood to be coming from the left kidney Retrograde pyelograms and intravenous pyelograms were normal His red cell count was 3,200,000 with 6 8 gm of hemoglobin He was given five transfusions of citrated whole blood No diagnosis was established He was dismissed on November 29, 1947 at his own request The hematuria was still present but was less than on admission

He was seen again on December 12, 1947 in the outpatient department The hematuria had persisted and he was readmitted to the hospital He was obviously anemic, quite dyspneic on the slightest exertion and complained of marked palpitation The pain in his left side had become more acute and radiated to the lower left quadrant of his abdomen

Except for the usual childhood diseases he had always enjoyed good health until the onset of the present illness He stated that he had many nosebleeds when he was a boy in school and that they always responded to home treatment

His mother was living and well, his father died many years ago of unknown causes He has 5 brothers and 8 sisters, all living and well All of his brothers had profuse and frequent nosebleeds during adolescence He had lost track of most of his family and the history was not accurate An attempt was made to contact members of his family but none would submit to examination

The temperature was normal, pulse, 98, respiration, 26, blood pressure, 102/58 in each arm The conjunctivas and the mucosa of the lips were quite pale There were no telangiectases found Lungs were clear and resonant to percussion and auscultation There was a soft blowing systolic murmur The heart was of normal size. There was moderate tenderness in the left flank and costovertebral angle. No abdominal viscera were palpable. The remainder of the physical examination was essentially normal.

The urine was grossly bloody. Specific gravity, 1.010; pH, 5.5; albumin, 3 plus; sugar, negative. There were innumerable pus cells per high power field in a noncentrifuged catheterized bladder specimen. Smear of urine sediment for tubercle bacilli was negative. Culture for tubercle bacilli was also negative. The red blood cells numbered 2,290,000 with 5.9 gm. hemoglobin. Platelets, 276,000; white blood cells, 10,950 with a normal differential count. There were 4.8 per cent reticulocytes. Urine culture from the right kidney showed no growth; culture from left kidney showed Alkaligenes faecalis. Blood Kahn was negative. Bleeding time, 1 min., 30 seconds; coagulation time, 5 minutes; clot retraction time, normal. Prothrombin time, normal; sickel cell preparation showed no sickling at the end of 24 hours. Red cell fragility test, normal. Liver function tests were normal. The tourniquet test was negative at the end of 15 minutes in each arm. X-ray of the chest was normal.

During this hospital course his temperature remained normal. He was placed on ferrous sulphate and was given an additional transfusion. There was little benefit from this therapy. He continued to have profuse gross hematuria. Two cystoscopic examinations done a week apart again revealed the blood to be coming from the left kidney. On January 7, 1948, a subcapsular nephrectomy was performed. The kidney specimen was grossly normal.

The gross specimen was a kidney measuring 11.5 by 5.5 by 2.5 cm. and weighing 140 gm. The capsule was absent. The surface was reddish-brown and smooth. There were two small hemorrhagic areas on the surface, one measuring 1 mm. in diameter and the other 2 mm. They were dark reddish-purple in color.

On cut section the kidney was reddish-brown in color. The cortical thickness varied from 6 to 7 mm. The cortical striations were plainly seen.

The pyramids were slightly pale in color. Numerous small, dark purple, circular spots were seen in the pyramids. The first of these spots, 1 mm. in diameter, was observed in the pyramid emptying into the most superior calyx 1.4 cm. from the surface and 2 cm. from the upper pole and .8 cm. from the calyx. A second dark spot, 2 mm. in diameter, was observed in the pyramid emptying into the third calyx from the superior pole. This spot was 1.1 cm. from the surface and 0.8 cm. from the calyx. A third spot was observed in the next most inferior pyramid emptying into the fourth calyx from the superior pole. This spot was 1 mm. in diameter, 1.4 cm. from the surface of the kidney and 0.7 cm. from the calyx. Another spot, 3 mm. in diameter, was observed in the other half of the calyx. It was 1.5 cm. from the surface and 2 mm. from the calyx. A spot 1 mm. in diameter was observed in the pyramid emptying into the fifth calyx from the superior pole. This spot was 1.5 cm. from the surface and 1 mm. from the calyx.

The calyces, pelvis and ureter were normal.

Microscopic sections showed essentially normal renal tissue. In several sections there were some large blood vessels in the region of the collecting tubules which had very thin walls with no muscular coating (fig. 2).

Except for a rise in temperature to 102 F on the second day, and moderate gaseous distention of the abdomen the postoperative course was uneventful. The hematuria disappeared on the second day. The patient showed immediate improvement in his morale but he was cautioned that his other kidney might bleed from the same cause at some later date. He was discharged on the fourteenth postoperative day.

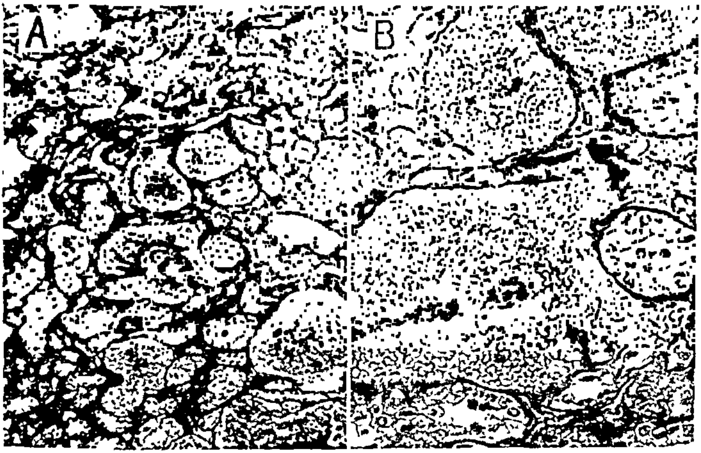

FIG. 2. Case 2. *A*, section through telangiectatic area of kidney, showing marked dilatation of capillaries and absence of muscular coat. × 100. *B*, same section. × 400

He has been seen at weekly intervals since his discharge. His hemoglobin is now 12.5 gm. and red cell count 4,580,000. He has returned to his previous occupation and states that he feels well and has had no more hematuria.

COMMENT

It was only after much deliberation that the kidney in the second case was removed. Nephrectomy was considered justified because of repeated attacks of unilateral hematuria proved by cystoscopy during the episodes of bleeding. The patient was profoundly depressed mentally and in a state of chronic anemia. Multiple blood transfusions and other supportive measures were of no avail.

It is believed that many cases of undiagnosed renal hematuria may be classified as hereditary hemorrhagic telangiectasia if a careful history is elicited with regard to familial bleeding and a careful search is made for the typical lesions of the skin, nose and mouth.

The kidney in case 1 was not removed because blood was seen to come from the right ureter in one examination.

SUMMARY

A brief review of the literature concerning hereditary hemorrhagic telangiectasia with hematuria is presented.

Two additional cases of hereditary hemorrhagic telangiectasia with hematuria are reported. In one a nephrectomy was performed.

103 W. Brookwood Dr., Valdosta, Ga.

The Journal of Urology
Vol 62, No. 1, July 1949
Printed in U.S.A.

INTRACAINE LUBRICANT AS A URETHRAL ANESTHETIC[1]

BUDD C. CORBUS

While visiting Dr. Reed Nesbit's clinic at the University Hospital in Ann Arbor, I was impressed by his technique of producing urethral anesthesia for cystoscopies and urethral instrumentation. Nupercaine was incorporated in a lubricant, the substance being packed in a collapsible tube containing just enough material for one instillation. The urethra was filled, taking great care to massage the anesthetic into the posterior urethra. A urethral clamp was placed over the glans penis thereby holding the lubricant in situ. In 5 or 6 minutes the patient was ready for cystoscopy.

Dr. Nesbit was kind enough to let me have the formula for the lubricant, but on returning home I found it was no longer possible to buy nupercaine crystals on the market. Through the cooperation of Mr. R. C. Anderson of Squibb and Company and Mr. E. H. Devine of Lyman's Pharmacy it was suggested that intracaine in a 2 per cent solution be substituted. The following is the formula of intracaine lubricant:

Intracaine hydrochloride (Squibb)	20 0 gm.
Phenol liquefied (U.S.P.)	5.0 cc
Boric acid (U.S.P.) .	80 0 gm
Tragacanth (Ribbon-U.S.P.)	40 0 gm.
Glycerin (U.S.P.) .	200.0 cc
Distilled water to make .	1000 0 cc

Intracaine (Squibb's Diethoxin) was introduced by McIntyre and Sievers in 1937. It is not new; however, up to the present time it has had little publicity. It is a benzol derivative and has been compared with procaine hydrochloride for injection anesthesia.

Belt and Bavetta report that they have used intracaine hydrochloride in 2 per cent solution instilling 5 cc or more in the urethra in 13,200 cystoscopies and in over 5,280 urethral dilations with not a single toxic reaction. They state further that intracaine's chief virtue, in addition to its low toxicity, is the duration of the local anesthesia which contributes much to the post-instrumental comfort of the ambulatory patient.

Bumpus reports favorable results in its use, especially when the urethra has been traumatized or when there is any question of idiosyncrasy to cocaine.

Douglas, using 1 to 1½ per cent solutions, has injected the kidney pelves and bladder at the same time with no untoward effects. In man and in animals intracaine hydrochloride is effective in about one-half the strength of the usual local anesthetics (procaine hydrochloride). Its action is quicker and more uniform and lasts a longer time. It definitely tends to spread to a greater degree beyond the immediate zone of infiltration. It does not lose its anesthetic power on boiling.

---

[1] Read at meeting of Chicago Urological Society, January 23, 1947.

Like other anesthetics of this type, intracaine can be used for spinal, sacral and infiltration anesthesia. It also comes commercially under the trade name of Intracaine In Oil. Excluding cystoscopies it is very valuable in ordinary instrumentation.

Intracaine lubricant has the following advantages:—

Due to the phenol that is incorporated in the lubricant it is absolutely sterile. This has been proven by myself as it was impossible to culture any bacteria from jars or tubes that were in my daily use.

Intracaine lubricant is water soluble and will not fog cystoscopic lenses.

Intracaine lubricant coats the urethra like a paste and thereby enhances its anesthetic action. Its close adhesion to the mucosa permits its continued action after the instrument has been withdrawn, thereby greatly lessening tenesmus and strangury that invariably accompanies urethral instrumentation.

636 Church St., Evanston, Ill.

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Bumpus, H. C., Jr.: J. A. M. A., 123: 615, 1943.
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Vol. 62, No. 1, July 1949
Printed in U.S.A.

IMPLANTER FOR RADON SEEDS FOR USE WITH THE McCARTHY FOROBLIQUE PAN-ENDOSCOPE

J. ROBT. RINKER

From the Department of Urology, University of Georgia School of Medicine, Augusta, Georgia

An implanter for radon seeds has been modified so that the shaft is rigid and can be used with the McCarthy Foroblique Pan-Endoscope. With this instrument, the seeds can be implanted with greater ease, accuracy, and speed in that portion of the bladder which is accessible through the McCarthy Foroblique Pan-Endoscope (fig. 1).

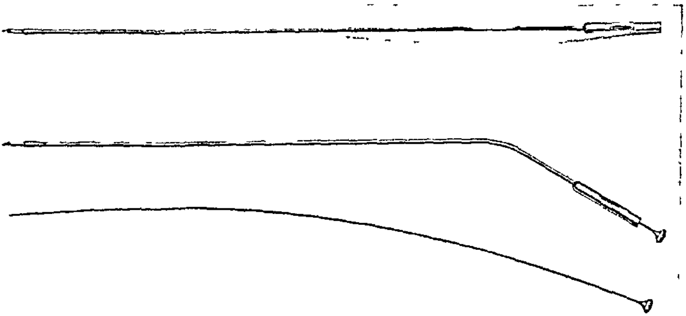

Fig. 1

There are a few elementary points which might be mentioned regarding its use. When the seed is inserted in the slot, the inflow of water should be stopped and the outflow cock opened, so that the seed will not be washed out. The operating fin can be used and facilitates in accurately guiding the point of the instrument. Inasmuch as the manufacturers have not yet insulated a cystoscope so that a metal instrument will not short out the light when it reaches back as far as the light cord contact, it will be helpful to slip a piece of gauze or some other insulating material between this and the implanter, as is done when using other metal instruments, such as stone extractors, cystoscopic forceps, etc.

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William Stewart Halsted

1852-1922

Dr. Halsted was one of the "old guard" at Johns Hopkins; a man of quiet, modest, unassuming per- [illegible] the intel- [illegible] reported [illegible] credited with the introduction of rubber gloves in 1890. His refinements in surgical technics have had wide influence.

Dr. Halsted received his A.B. at Yale in 1
M.D. at Columbia in 1877. Post-graduation
ied at Vienna, Leipzig, Wurzburg. In the 18
was attending surgeon at Bellevue, Presbyter
Roosevelt Hospitals, New York.

In 1889 Dr Halsted accepted the chair in
at Johns Hopkins University, Baltimore. He
conspicuous example of the great surgical tea

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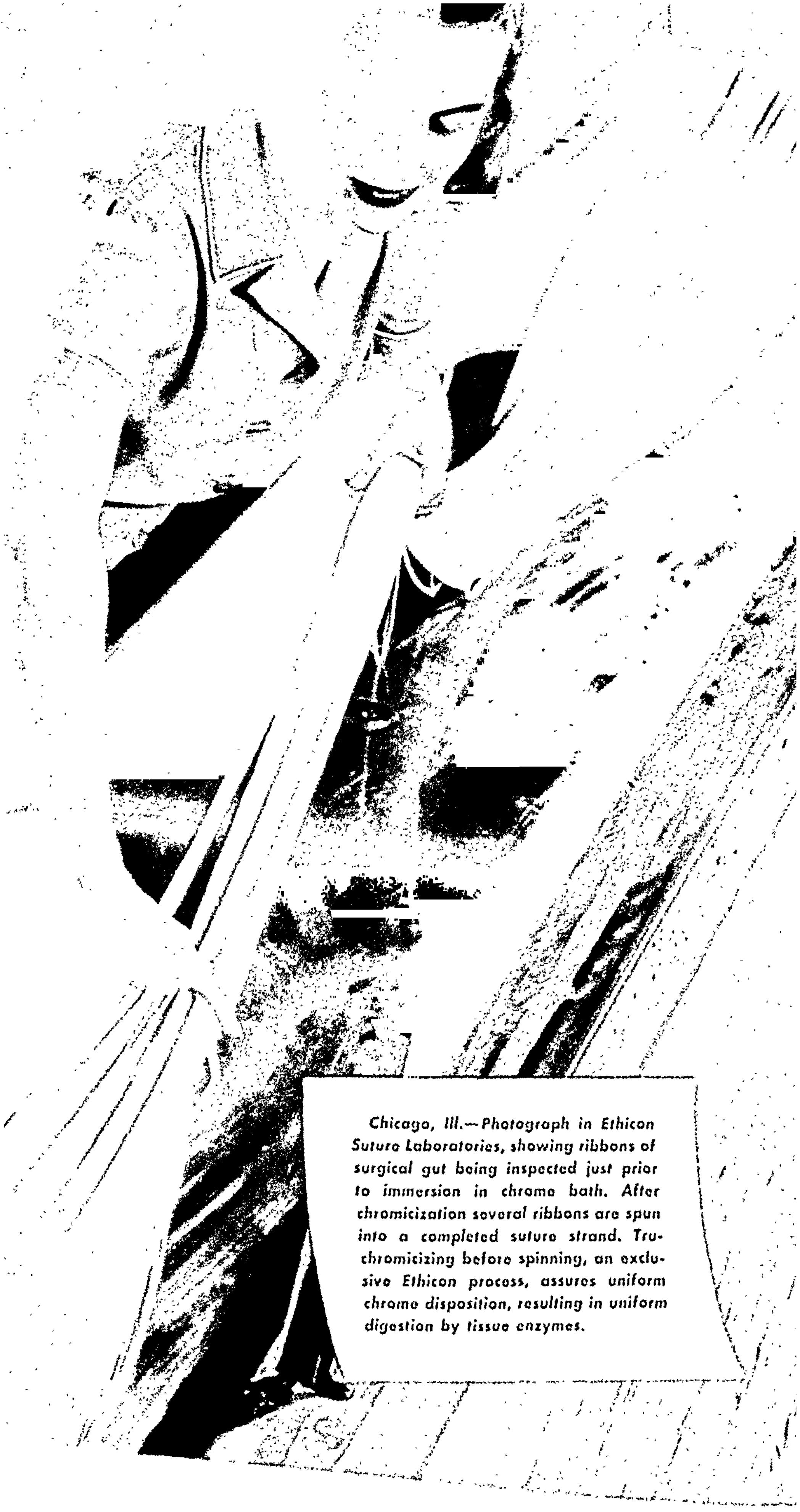

Chicago, Ill.—Photograph in Ethicon Suture Laboratories, showing ribbons of surgical gut being inspected just prior to immersion in chrome bath. After chromicization several ribbons are spun into a completed suture strand. Tru-chromicizing before spinning, an exclusive Ethicon process, assures uniform chrome disposition, resulting in uniform digestion by tissue enzymes.

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1. Sufficient chrome content to withstand premature digestion.
2. Chrome concentration must not be so excessive that fragments of the suture resist digestion and persist in tissue. This condition frequently leads to knot extrusion.

In order to obtain a product having the highest possible degree of uniformity, Ethicon chromicizes raw gut strands in the ribbon stage. This more meticulous process was named Tru-chromicizing. The alternative method, used by others, called surface-chromicizing, involves the dipping of the finished, spun and dried suture strand in a chrome bath. These are the results of the two methods:

Surface-Chromicizing

In enzyme solution, the core of most surface-chromicized gut digests readily, leaving a hollow cylinder which separates into ribbons.

This cylinder may be excessively resistant to enzyme action and remain as an undigested foreign body indefinitely.

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2. High tensile strength of suture retained for the healing period, followed by complete absorption.
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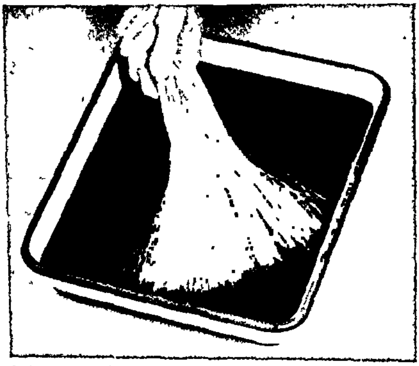
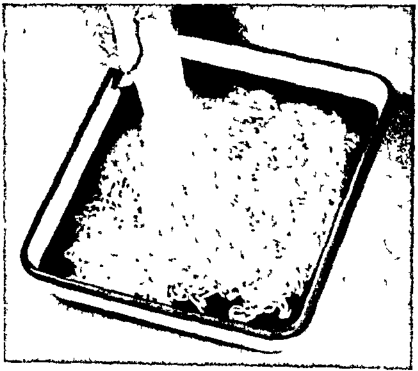


When gut is chromicized after strands are spun and dried, chrome concentration is very high in surface layers and relatively low in the core. Inner core is digested rapidly—the highly chromicized periphery survives for prolonged periods.

ETHICON TRU-CHROMICIZING



Individual ribbons of gut are soaked in chrome bath before they are spun into strand, permitting uniform deposition of chrome. The strand thus has the same chrome content from periphery to center.

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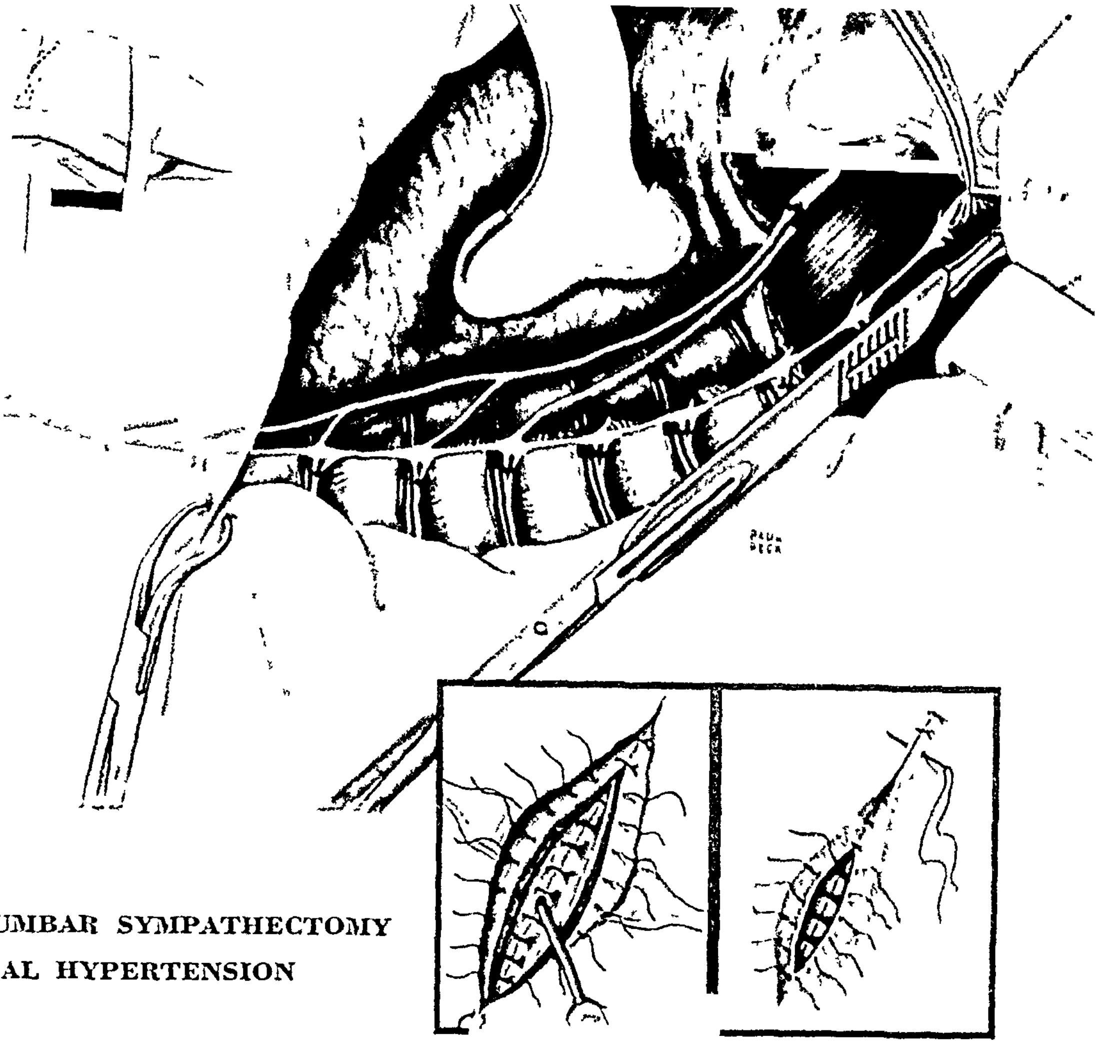
*To illustrate this comparison, small laboratory trays are used. In commercial production, surface-chromicizing is done under tension. Both processes are performed in large vats.



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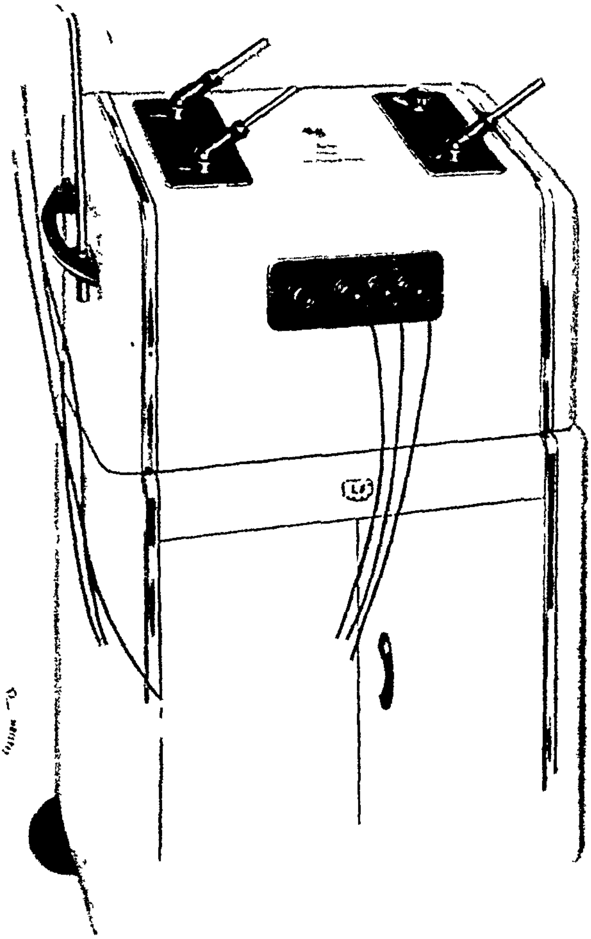

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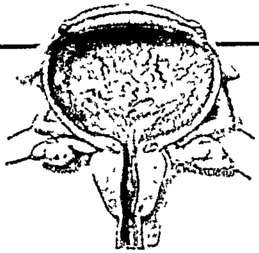

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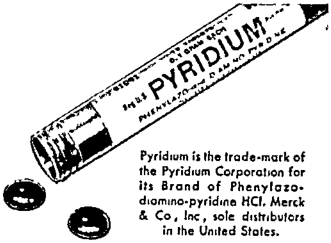

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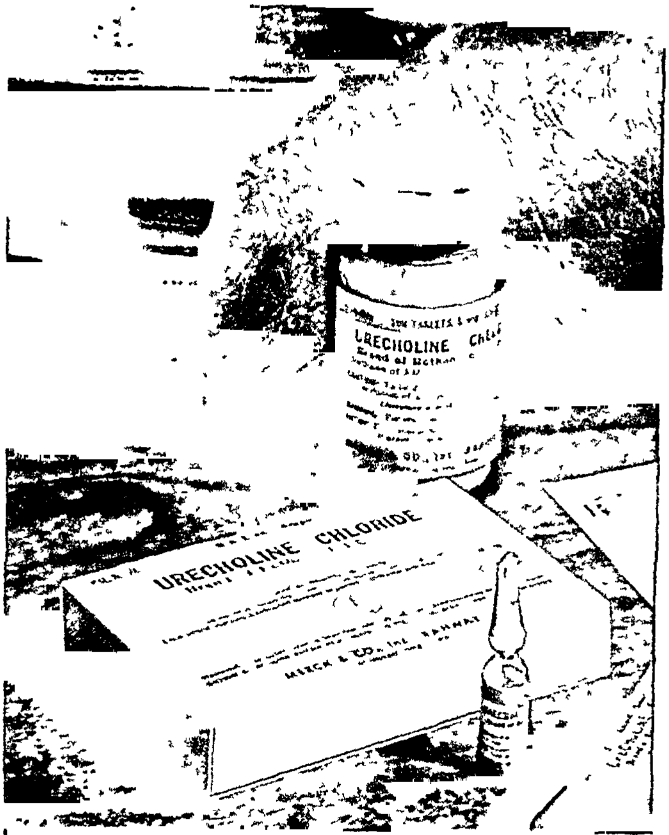

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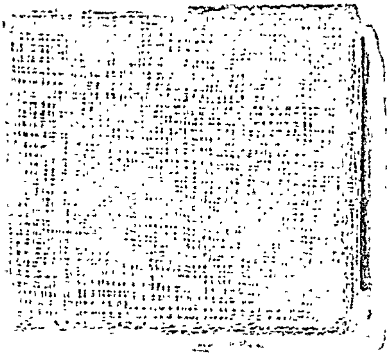

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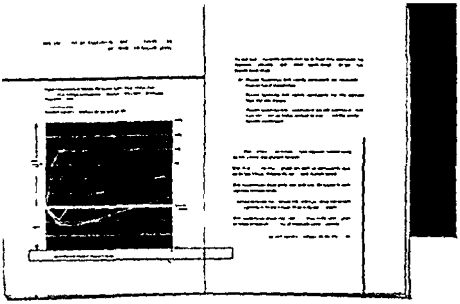

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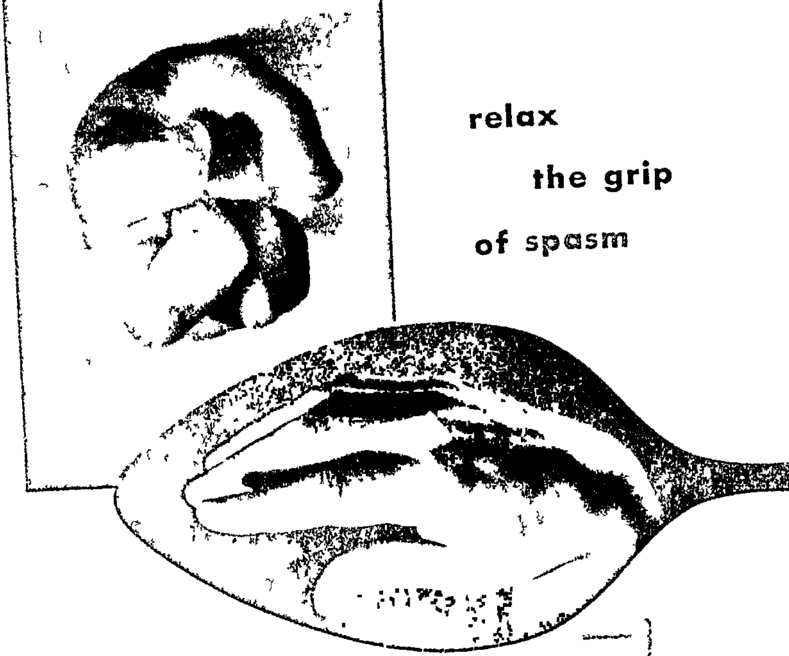

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1. Kilstein, R. I., Rev. Gastroenterol., 14.171, 1947.
2. Morrissey, J. H., J. Urol., 57 635, 1947.
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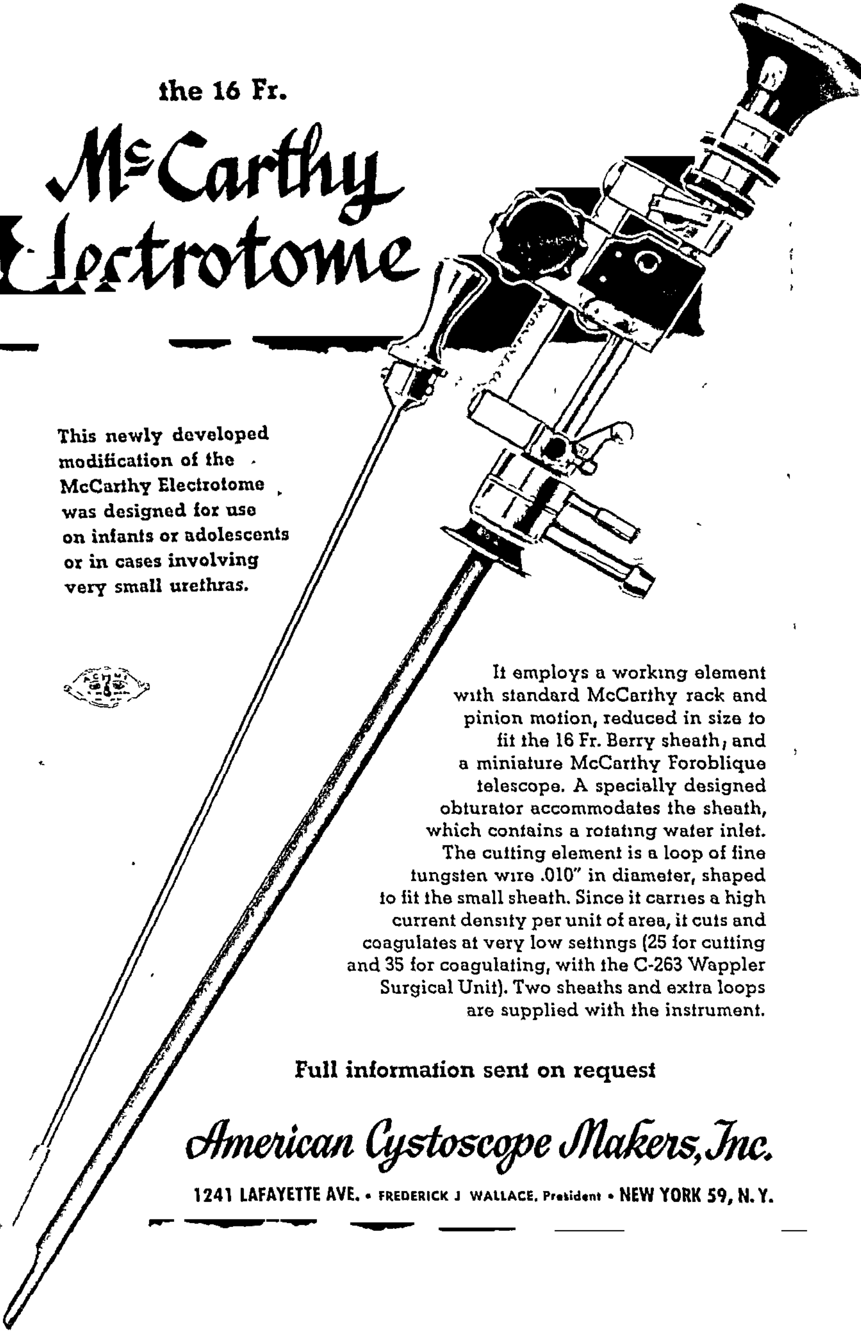

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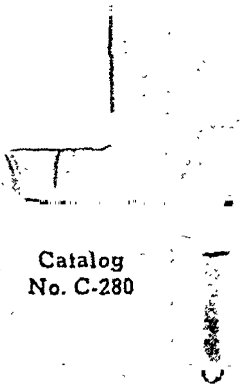

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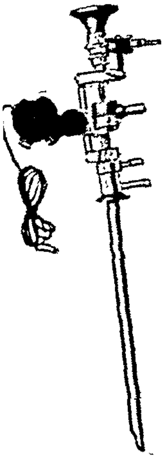

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CHRONIC PARATYPHOID PYELONEPHRITIS CURED BY NEPHRECTOMY: REPORT OF A CASE WITH A TRIAL OF STREPTOMYCIN

FREDERICK C. McLELLAN AND HERMAN J. BREZING
From the Division of Surgery (Urology), Grasslands Hospital, Valhalla, N. Y.

A case of chronic paratyphoid pyelonephritis with calculi cured by nephrectomy is reported. This case was studied under sulfadiazine and streptomycin therapy prior to surgery. A review of the American literature shows only one description in 1930 of the urinary infections by the paratyphoid bacillus (Barker).

DISCUSSION OF THE PARATYPHOID INFECTIONS OF THE GENITO-URINARY TRACT

History. Salmonella paratyphi were first described by Gilbert in 1893 as paracolon bacilli, to designate a group of intestinal bacteria which seemed to be intermediate in the typhoid colon group. Study of 91 articles since that date, on Salmonella in reference to the present case report, shows that infections by these organisms have been most extensively described in the German literature. This fact is largely explained by the great epidemics of this organism in Germany during the first World War and in Russia following the first World War (Bumke; Fain). Korns states that most chronic paratyphoid carriers in the United States at the present time are immigrants. Recently, special attention has been given these bacilli, and three Salmonella Centers have been established in the United States. One of these centers (Seligman, Saphra and Wassermann) has isolated more than one hundred types of Salmonella in the United States. This partly explains the varying clinical picture that this group of bacteria presents. The A type of paratyphoid bacilli tends to resemble the typhoid bacillus, but types B and C come closer to the B. coli group, according to Gay. While vital statistics (Linder and Grove) show that the mortality rate for typhoid and paratyphoid infections in the United States has fallen from 31.3 to 1.1 per 100,000 population from 1900 to 1940, the mortality rate in 1916 Salmonella cases reported in 1946 was 5 per cent (Seligman, Saphra and Wassermann). The importance of eliminating carriers of paratyphoid was shown by Ledingham and Arkwright when they stated that man is the sole reservoir of paratyphoid A; and, while other Salmonella occasionally occur in animals also, a single type is rarely pathogenic for both man and animals. The chronic urinary carrier state tends to be less common in paratyphoid than in typhoid infections. Leishman found one chronic urinary carrier in 546 cases of typhoid fever and two chronic urinary carriers (one was fecal and urinary) in 2262 cases of paratyphoid fever. Bumke found that approximately 60 per cent of chronic urinary paratyphoid carriers also excreted bacilli in the feces and that S. paratyphi A involved the urinary tract more frequently than S. paratyphi B. Worster reports that paratyphoid B has a marked tendency toward pus formation throughout the body. Barker felt that paratyphoid urinary infections differed from typhoid infections in that the urine tended to have a foul odor and that they were more persistent with more clinical symptoms. Although the French feel that paratyphoid B may begin primarily in the bladder (Roch), this is not generally accepted (Weis).

Pathology. The urinary pathology caused by the paratyphoid bacilli is listed by Bumke as follows: a) toxic nephrosis; b) toxic glomerulonephritis; c) miliary kidney abscesses (secondary infections of the urinary ducts, solitary abscess, perinephric abscess, pyelonephritis with eventual stone formation, pyonephrosis); d) abscess in the testicle or prostate (secondary epididymitis, seminal vesiculitis, urethritis). Abramson has shown that women may have vulvar infection from infected feces with sterile urine on catheterization. Barker feels that ascending infection is common in women. Fain found 44 per cent renal involvement in 268 fatal cases of paratyphoid fever: 68 with multiple cortical abscesses, 31 with acute parenchymatous nephritis, 12 with multiple scars from abscesses, 9 with acute glomerulonephritis, 1 with purulent pyelonephritis, and 6 with acute cystitis. Foley, Faille and Brandon report cases of mixed infections with paratyphoid A and B and typhoid bacilli. Bumke showed that chronic pyelonephritis, hydronephrosis, pyonephrosis, calculi, tuberculosis, cancer, and deformities predisposed toward renal involvement, and that urinary pathology was present in most cases of chronic bacilluria. Patch feels that renal calculi can probably develop either before or after typhoid infection.

Garbat showed that typhoid bacilli could be present in the urine with no detectable change on urinalysis, probably due to a simple filtration of the bacilli through the kidney without pathologic change and with multiplication in the renal pelvis and bladder without inflammation. Steinthal reports a chronic case, in which the absence of disease was confirmatory to this concept. However, Patrick favors the rupture of microabscesses in the kidney as a probable cause of most bacilluria. Garbat also showed that the excretion of typhoid bacilli in the temporary carrier may be remarkably intermittent, with bacilluria on catheterized specimen at 6 and 8 a.m. but none at 7 a.m. He showed that the catheterized urinary bacterial count can vary from 36,000,000 to 100,000 per ½ cc of urine in 3 hours. In addition, he demonstrated that bacilluria in a temporary carrier did not recur after a remission of 48 hours, by means of 24 hour urine cultures. Bassler is of the opinion that paratyphoid carriers occasionally give no history of previous clinical disease. A chronic urinary carrier may show recurrent systemic infection when his immunologic response is poor (Ledingham and Arkwright). Bumke found bacilluria beginning as late as 3 months after the original paratyphoid infection, and he showed that approximately 80 per cent of temporary convalescent paratyphoid urinary carriers recovered spontaneously within one half year.

Treatment. In evaluating the literature regarding therapy for paratyphoid urinary infections, the temporary carrier for less than one year must be excluded from the chronic carrier, since the temporary carrier has a marked tendency toward spontaneous remission without therapy (Browning). Crowley and O'Conor feel that lymphatic channels connect the urinary and intestinal tracts, and that frequently urinary excretion can be cured when intestinal infection is controlled. Barker states that urotropin, helmitol, and hexylresorcinol are ineffective and that intravenous neoarsphenamine and mercurochrome produce inconstant effects. He reports the cure of a chronic paratyphoid B cystitis in a woman with 2 per cent silver nitrate irrigations after the method recommended by Schottmuller for the bladder and even for the renal pelvis. Browning had no success with acriflavine. Murakami mentions three cures by intravenous trypaflavine and intravenous tetra iodgnost. Fraser and Faulds report a case in which vaccine treatment failed.

Brekke describes a urinary paratyphoid B carrier who had 10 colonies in the urine from the left kidney and 1000 colonies in the urine from the right kidney. He felt that the left kidney culture was a contaminant, and he performed a right nephrectomy. Bacilluria continued for 2 months postoperative before a cure was obtained. In a report on Salmonella infections, Seligman, Saphra and Wassermann mention that a urinary S. cholerasuis infection was cured by nephrectomy. Fain recommends conservatism in surgery after observing a case, treated by nephrectomy, that later expired from focal abscesses in the remaining kidney. Nephrectomy in indicated cases has given excellent results in the urinary typhoid carrier state with more than 75 per cent of the cases cured (Browning).

CASE REPORT

P. V., No. A5566, a man, aged 54, single, was transferred from a neighboring hospital to the psychiatric service of Grasslands Hospital on January 9, 1947 for toxic exhaustive malnutritional psychosis. The patient was born at Mongrando, Italy (near Piedmont) on October 3, 1892. At 12 years of age, he had an attack of "typhoid fever", treated by a milk diet for 3 months, and characterized by weakness, fever to 104 F., headache, slight vomiting, no diarrhea and no urinary symptoms. Thereafter, his mother suffered with a similar illness for 1 month. He made a complete symptomatic recovery, but, at the age of 20 years, he first noticed an occasional nonradiating catch in the left lumbar area, unrelated to time or activity. He noted an increase in the left sided back pain during the past 10 years; but he had no hematuria, frequency, urgency, dysuria, nocturia, or eneuresis until his present admission, when he noted, for the first time, slight dysuria and nocturia 1 time.

He served in the Italian Army in the Alps from 1915 to 1919, where he probably received antityphoid vaccine. He migrated to the United States in 1920 and lived at New Britton, Conn. until 1935. Here he worked as a plasterer, cement finisher and fireman. He cleaned "silver" in a kitchen in New York City from 1935 to 1938. During the next 9 years, until his present admission, he worked in the kitchen of a large restaurant in New Rochelle, N. Y. preparing salads and fresh oysters. The Westchester County Board of Health reports no case of paratyphoid A infection during the 9 years that he handled food in that county. No evidence can be elicited from the patient and his employer in favor of an infectious state.

During hospitalization elsewhere in 1942, 1943, 1945 and 1946 for leg ulcers, he had 8 urinalyses, which varied from 8 to 400 white blood cells per high power field with zero to 2 plus albumin and no red blood cells. During 113 hospital days for the leg ulcers, he had no unexplained pyrexia, and no further contributory information was learned.

His past history showed that he had an undiagnosed illness, 15 years ago, for 1 month, characterized by weakness and occasional fever, but not interfering with his occupation. The remainder of his past history and the family history were negative.

On December 13, 1946, he was brought to a neighboring hospital by ambulance for progressive weakness. Marked mental cloudiness made the history unsatisfactory at this time, and physical examination showed evidence of malnutritional psychosis. He showed gradual improvement on a high vitamin diet, and, on January 9, 1947, he was transferred to Grasslands Hospital for toxic exhaustive malnutritional psychosis. A urine culture on December 23, 1946 was positive for Salmonella paratyphoid A.

The patient was pale and undernourished. His temperature was 99.2.F, pulse 90, respirations 24, and blood pressure 130/100. The tongue borders were atrophic; the lungs were clear to percussion and auscultation; the heart was normal to palpation, inspection, percussion and auscultation; the abdomen was negative with no palpable kidneys and no costovertebral angle tenderness. The genitalia were normal and the prostate was normal in size, smooth, and firm. A brown pigmentation was present over both lower legs. The neurological examination showed no sensory or reflex changes.

A blood count showed 3,450,000 red blood cells, with 10.5 gm. hemoglobin, 6,560 white blood cells with 58 per cent neutrophils, 34 per cent lymphocytes, and 8 per cent monocytes. Urinalysis showed a specific gravity of 1.014, acid reaction, 2 plus pus and no red cells on microscopic examination. Three urine cultures were positive for Salmonella paratyphoid A. The Wasserman test was negative, as was an examination of the spinal fluid. The nonprotein nitrogen was 33. Four stool cultures were negative. Serum agglutinated with antigen of E. typhosa "O" 1-320, E. typhosa "H" 1-40, S. paratyphi A 1-40, S. paratyphi B 1-40, Br. abortus -0, on two occasions. Two 24 hour urine specimens showed no tubercle bacilli on culture. The residual urine in the bladder was 40 cc. The phenolsulphonphthalein test showed 68 per cent excretion of the dye in 2 hours. Intravenous pyelogram revealed several calcific deposits over the lower part of the left kidney shadow. The left kidney showed considerable blunting of the minor calyces. Retrograde pyelogram showed calculi in the inferior calyces of the left kidney. On cystoscopy, the bladder mucosa was slightly injected and granular. No additional alterations were noted aside from slight intrusion of the middle lobe of the prostate. Ureteral catheterization on three occasions showed 25 white blood cells per high power field from the left kidney with a positive culture for S. parapyphi A, while the right kidney was normal.

A diagnosis of left chronic paratyphoid A. pyelonephritis with calculi was established.

The patient received two courses of sulfadiazine gm. 1, and sodium bicarbonate gm. 4, four times daily, for a total of 40 days. During sulfa medication, with blood levels recorded at 4.6 and 2.1 mg. per cent, his urine remained sterile. Six days after therapy, paratyphoid A could again be constantly cultured from his urine.

The left renal calculi were deemed a barrier to chemotherapy for his paratyphoid bacilluria. A ureteral irrigating catheter was placed in the left kidney pelvis, and continuous irrigation with Suby G solution was administered on two occasions. However, the patient removed the catheter during his sleep, in less than 24 hours on each occasion, for no apparent reason.

The paratyphoid bacilli were sensitive to 7.8 and 3.9 micrograms of streptomycin on two in vitro tests, and he received streptomycin 0.375 gm. every 3 hours, for 10 days, with blood levels recorded at 11.6 and 44.2 micrograms per cubic centimeter. During the last 2 days of this therapy, sodium bicarbonate gm. 3 every 4 hours, was added to the streptomycin. Again the urine promptly became sterile, but the paratyphoid bacilluria recurred in 8 days after therapy. The patient agreed to nephrectomy for the persistent paratyphoid infection of his left kidney, and he made an uneventful recovery from a left nephrectomy, done on May 29, 1947. Sulfadiazine gm. 1 and sodium bicarbonate gm. 2, with penicillin 30,000 units every 3 hours, were given routinely for 1 week postoperative. The bacilluria was still found on culture on the fourth postoperative day, but, thereafter 5 consecutive urine cultures were negative. He was discharged recovered on June 20, 1947.

The gross specimen consisted of the left kidney and the proximal 6 cm. segment of ureter. The specimen was of about normal size and shape with a weight of 200 gm. The capsule was thin, but stripped with difficulty from the underlying coarsely nodular cortical surface. On cut section, the normal renal architecture showed marked distortion with obliteration of all gross differentiating features between cortex and medulla. The shell of the renal parenchyma varied in thickness from 0.5 to 1.0 cm. and formed a narrow band over the dilated calyces. The pyramids were blunted or often completely obliterated. Peripelvic fat was present in excess and comprised approximately half of the bulk of the specimen. The calyces were cystically dilated, while the pelvis and ureter figured little in the dilatation. The mucosa of the ureter and pelvis, however, was coarsely granular, lusterless, and of leathery consistency. Several fine, flaky, mottled yellow and black, soft calculi were present in the calyces and ureter.

On microscopic examination the renal parenchyma reflected changes of a chronic inflammatory nature. The mucosal and submucosal tissues of the ureter and pelvis were rather richly infiltrated by lymphoid and plasma cells. Neutrophiles were rarely encountered. While a generalized increase in the renal interstitial tissue was noted, such changes were particularly evident in small discrete focal areas in the cortex. Here the glomeruli were hyalinized, the tubules obliterated, the fibrous interstitial tissue overgrown and showed an influx of lymphoid cells and small recent hemorrhages. Many tubules contained an amorphous acidophilic coagulum. A few were cystically dilated. The tubular epithelial cells were often swollen with coarsely granular cytoplasm. The glomerular tufts, too, were swollen and somewhat congested, but reflected little structural alteration except in the above noted cicatricial areas. Amorphous coagulum filled many of the subcapsular spaces. The arteries and arterioles manifested a moderate degree of sclerotic change. Note: S. paratyphi A was cultured from the renal pelvis. Diagnosis: chronic pyelonephritis of left kidney due to S. paratyphi A.-renal calculi.

Follow-up of this patient showed negative urine cultures on July 1, August 5, December 9, 10, 12, 1947 and April 24, 1948, eleven months postoperative. His nonprotein nitrogen was 39 mg. per cent and his phenolsulphonphthalein test showed 60 per cent excretion in 2 hours on April 23, 1948. On December 12, 1947, he had a subtotal gastrectomy for a large ruptured duodenal ulcer that could not be closed, with uneventful recovery. This clinical and laboratory evidence shows little, if any, impairment of total renal function after the nephrectomy.

DISCUSSION

Streptomycin. No reference concerning the use of streptomycin in Salmonella urinary tract infections has been found in the literature. Keefer et al. found varying results in streptomycin therapy of the systemic Salmonella infections, depending on the variation in susceptibility of various strains to streptomycin (0.5 to 60.0 micrograms per cubic centimeter recorded), the localization of the disease, and the presence of other disease. Pulaski states that streptomycin in adequate dosage for 5 days is effective against urinary infections by organisms inhibited in vitro by a concentration of 16 micrograms of streptomycin per cubic centimeter, when no organic disease, such as calculi or hydronephrosis, is present. Escherichia coli urinary infections showed some of the best results in streptomycin therapy, especially with alkaline urine. Clinical, bacteriological and pathological considerations have led Gay and also Pick to place Salmonella paratyphi midway between the Eberthella typhi and Escherichia coli groups of organisms. While the strain of S. paratyphi A in this case was inhibited in vitro by 7.6 and 3.9 micrograms of streptomycin on two occasions, and while blood levels of 11.6 and 44.2 micrograms per cubic centimeter were recorded during 10 days of therapy, the urine was only temporarily bacillus free, probably because renal calculi and chronic pyelonephritis were also present.

Sulfadiazine. The temporary removal of paratyphoid bacilli from the urine by sulfadiazine, in this case, would also tend to show the effectiveness of this drug in suitable cases. Similar results have been noted in carriers of E. typhi in certain cases (Barer). The combined use of sulfadiazine and penicillin has given varying results (Harris and Meyers; Gordon and Shechter). However, the failure of sulfadiazine to achieve permanent cure, in spite of therapy for 40 days, would add further evidence that surgery rather than drug therapy is indicated when organic pathological change such as calculi, is present.

Unilateral renal involvement. No definite reason can be given for the unilateral renal involvement in this case. The possibility that renal calculi were present prior to the paratyphoid infection, seems unlikely, since the patient was 12 years of age at the time of the initial infection, and since the pathologist's report indicates a similarity between the calculi and the amorphous debris in the renal tubules. That the original disease affected one kidney more severely than the other cannot be excluded.

Indications for nephrectomy. Bumke states that nephrectomy will cure the chronic urinary carrier of S. paratyphi when the organism can be cultured from only one kidney and when the organism is absent from the stool. Browning reports that while chronic urinary carriers frequently have few symptoms, they tend to develop serious disease as the duration of the infection increases. Repeated examination showed that the above criteria were present in this case, and nephrectomy was performed to allow the patient to return to his occupation as food handler, to free him from the surveillance of the health department and from the fear of infecting others, especially children, and to render disinfection of his urine necessary.

Carrier state. This case is unusual in that the patient worked as a food handler during the last 12 years when he was undoubtedly a chronic paratyphoid carrier, and yet there is no evidence of transmission of his disease. Although most paratyphoid epidemics have been traced to fecal carriers, Browning records the sole instance of transmission by a urinary carrier. He states that, while urinary carriers are more dangerous, because of the large number of bacteria present (often in pure culture), they may produce no transmission due to lack of virulence. This consideration is not proven, and it is possible that urinary carriers are not so dangerous when good personal hygiene and American methods of sewage disposal are practiced.

SUMMARY

A case of chronic left paratyphoid A pyelonephritis with calculi cured by nephrectomy is reported. A review of the literature shows that chronic urinary Salmonella infection is usually accompanied by serious organic changes, e.g., calculi or hydronephrosis.

Trial of streptomycin and sulfadiazine suggests that these drugs should be effective in a temporary paratyphoid bacilluria, but surgical excision is necessary for the underlying abnormality in the chronic carrier.

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SOLITARY PELVIC KIDNEY: A CASE REPORT[1]

OWEN C BERG AND WALTER M KEARNS

G C , aged 39 years, was first seen February 1, 1943, because his physician had found a trace of albumin in the urine on a routine examination The patient at that time was in good general health and had no complaints Past history and the family history were entirely negative General physical examination revealed a well developed young man who appeared to be in good health There were no abnormal findings and the blood pressure, pulse, and respiratory rate were all within normal limits Urinalysis revealed a trace of albumin and an occasional leukocyte However, examination of the urine voided on arising showed no albumin on several tests The blood nonprotein nitrogen was 30 mg per cent

On April 2, 1943, intravenous urography failed to visualize a kidney on either side, but the films were technically unsatisfactory It was recommended that the patient submit to a second examination including cystoscopy and pyelography, but he refused because of the lack of any physical complaints

The patient was next seen on May 8, 1948 Since his previous examination the patient had remained in good health and had lost no time from his work He had appeared for a periodic physical examination and had again been found to have albuminuria

Physical examination revealed a soft mass to the right of the midline just above the symphysis pubis which was slightly movable transversely The blood pressure was 124/82 Urinalysis revealed a trace of albumin and an occasional leukocyte, erythrocyte, and granular cast

Excretory urography was performed on May 9, 1948, and revealed no dye in either kidney fossa However, slightly to the right of the midline and at the level of the brim of the bony pelvis, a round, soft tissue mass was seen extending from the left margin of the lumbar vertebra approximately 2 inches beyond the right border of the vertebral body Within this mass, contrast medium appeared outlined a bizarre pelvis which had the shape of a crab, the renal pelvis suggesting the body of the crab and the calyces extending from either side as the claws The terminal calyces were not well visualized and the pelvis as a whole was slightly dilated The ureter drained from the most dependent part of the pelvis

Cystoscopy on May 10, 1948 revealed a normally formed right half of the trigone, but careful inspection both before and after the intravenous administration of indigo carmine failed to reveal the left side of the trigone or a second ureteral orifice A ureteral catheter could be introduced only 15 cm The excretion of indigo carmine was normal None appeared other than that which came through the ureteral catheter Retrograde pyelograms were made with the patient in the horizontal and in the deep Trendelenberg positions These films revealed no change in the position of the kidney (fig 1)

It is believed that periodic examination of this abnormally-placed kidney is indicated but that no other treatment is necessary at this time The man's activity is not restricted because of his condition

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[1] Read at annual meeting, North Central Section, American Urological Association, Des Moines Iowa, October 29, 1948

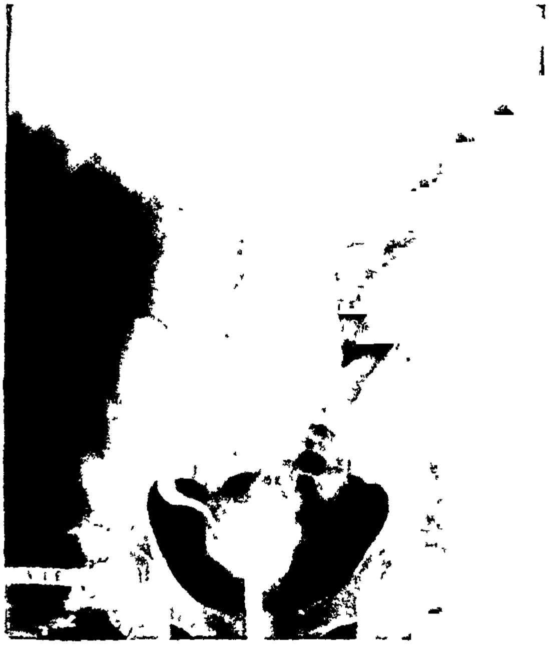

FIG. 1

TABLE 1.—*Supplement to previous tabulations of solitary pelvic kidney*

CASE NO.	AGE, SEX	GENITAL ANOMALIES	CLINICAL DIAGNOSIS	UROLOGIC FINDINGS
42 (Goldberg & Fowler, J. Urol., 47: 440–443, 1942)	51—M	None	Known to have ectopic kidney for 7 years prior to 1941. Living and well	Absence of left half of trigone. Intravenous pyelogram. Indigo carmine excretion *normal*
43 (Goodhope, Urol. & Cutan. Rev., 50: 268–269, 1946)	57—M	None	Clinical diagnosis of benign prostatic hypertrophy. Died 24 hours after rupture of bladder neck by sound before resection. No autopsy	Absence of right half of trigone. Excretory urogram revealed solitary pelvic kidney
44 (Vernek, Acta chir. Scandinav., 94: 99–110, 1946)	28—F	Absence of left adnexa	Laparotomy with preoperative diagnosis of torsion of ovarian cyst. Pelvic mass found to be kidney	Absence of left half of trigone. Excretory urogram revealed solitary pelvic kidney and dilated ureter above a small stone. Ureterolithotomy
45 (Berg & Kearns)	39—M	None	Clinical diagnosis of orthostatic albuminuria for 4 years. Repeat excretory urography refused by patient because asymptomatic	Absence of left half of trigone. Excretory and retrograde pyelography revealed absence of left kidney and deformed normally functioning right pelvic kidney

SUPPLEMENTAL TABULATION

The present case and three recently reported in the literature are presented in table 1 as a continuation of the previous tabulations of solitary pelvic kidney made by Stevens, 1937, McCrea, 1942, and Mays, 1946.

DISCUSSION

Although the condition of solitary pelvic kidney carries a considerable risk of early death from renal failure, it is not incompatible with life and many patients have been reported as carrying out a useful existence to old age. It is a condition, although uncommon, of which the general surgeon and obstetrician should be aware. Many unnecessary laparotomies have been performed in the presence of an unexplained pelvic mass which subsequently proved to be a pelvic kidney. In a few cases a pelvic tumor has been removed with fatal results when the mass proved to be the patient's *only* kidney. (Vernek describes most vividly how he almost removed such a "tumor" which biopsy revealed to be a solitary pelvic kidney.)

The obstetrician who is called upon to manage the pregnancy of a patient with a known solitary pelvic kidney is charged with a great responsibility in applying a safe method of delivery. To the urologist, the condition is one which calls for conservatism and considerable ingenuity when obstructive uropathy, calculus, or infection develop.

CONCLUSIONS

A case of solitary pelvic kidney has been reported in which the anomaly has been compatible with normal existence.

The literature has been reviewed. The present case and three recently reported have been added to previous tabulations bringing the total to forty-five.

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COMPLETELY FUSED PELVIC KIDNEY

SAMUEL D. KRON AND DAVID R. MERANZE

From the Department of Laboratories, Mount Sinai Hospital, Philadelphia

One of the rarest of urologic anomalies is a completely fused pelvic kidney. Only about 6 such cases can be found in the literature. An additional case is herein presented and the previous reports reviewed.

Bilateral renal ectopia is the rarest type of congenitally misplaced kidney encountered either clinically or at autopsy. Quinn stated in 1940 that a review of the literature, American and foreign, revealed that 28 instances of bilateral renal ectopia had been reported. Fowler in 1941 wrote that he had found reports of 40 cases. In this anomaly, both kidneys may be at the same or at different levels. Fusion may occur, but this is apparently rare. When fusion does occur, the conglomerate renal mass lies deep in the pelvis, forming the so-called lump, cake or shield kidney. In only 1 previous case does it appear that this latter type of anomaly was recognized clinically.

The first case of completely fused pelvic kidney that can be found in the literature is that reported by Looney and Dodd in 1926. The discovery was made during the dissection of a male cadaver, aged 70, and was associated with various anomalies of the abdominal viscera.

Thompson and Pace, in discussing 92 cases of ectopic kidneys in the records of the Mayo Clinic up to 1937, make mere mention of the fact that 2 of these cases were of the "cake" variety. Photographs of these 2 cases are presented. Shoemaker and Braasch gave descriptions of the gross pathologic changes in 35 cases of fused kidneys observed in the course of the necropsies performed in the Mayo Clinic during the years 1905 to April 1938. Again, only a note is made that "cake" kidneys were found in 2 cases. Without giving descriptions of these cases, they add that in 1 case the "cake" kidney was situated at approximately the normal level of the kidney and the other was situated in the true pelvis.

Eisendrath and Rolnick have the following notation under an illustration in their book: "Typical 'cake' kidney located in the true pelvis. This anomaly is the result of complete fusion along their mesial borders of the two halves of a horseshoe kidney. (Heiner's case)." Lowsley and Kirwin, in *Clinical Urology*, have diagrammed "asymmetrical fusion—'cake' kidney (Christeller)." E. C. Smith and L. Orkin, in a study of the congenital anomalies of the kidney and ureter in 18,460 cases, list 1 case of discoid kidney. No additional information is presented in any of these last three references.

Looney and Dodd described their case as a kidney consisting of a large mass lying over the right sacro-iliac joint and extending into the pelvis. The kidney was nearly circular in outline, possessing two distinct ureters, each measuring about 5 inches in length and opening normally into the bladder. The anterior or ventral surface of the kidney showed marked lobulation but no indication of a separation into right and left portions. The ureters arose separately from this anterior surface from 4 extrarenal calyces, which united about 1 inch from the kidney The posterior surface of the kidney was smooth and concave The blood supply consisted of three larger and several smaller arteries The left renal artery arose from the lower end of the left common iliac artery, the middle renal artery arose from the angle of the bifurcation of the aorta, the right renal artery from the proximal part of the right common iliac artery

In *Young's Practice of Urology* the description of "disc" kidney reads as follows "This condition, also called scutiform or shield shaped kidney, has a rounded, flattened shape As a rule it is situated lower than horseshoe kidney, at the pelvic brim or in the concavity of the sacrum and may be more to one side than the other It lies close to the posterior body wall and its posterior surface conforms to the structures with which it comes in contact The anterior surface is usually lobulated and from it arise the renal pelvis and ureters Its blood vessels pierce the posterior surface and are variable From the embryologic standpoint this type of anomaly bears a close relationship to horseshoe kidney, the fusion taking place along the whole of the medial border before rotation has been effected " Two recent discussions of congenital anomalies of the kidney and ureter, those of Culp and Hiebert, and Smith and Orkin list without detailed descriptions 1 and 2 cases respectively that could conceivably be similar to our case The latter paper is especially comprehensive, comprising a study of 18,460 consecutive urologic conditions, in which 471 instances of congenital anomalies were found H R Newman in 1946 reported a case that appears to have been similar to ours in most respects He described a congenital bilateral fused kidney, complicated by nephrolithiasis and pyonephrosis His case differed from ours in that there was apparently no communication between the renal pelves

CASE REPORT

M H , a white man aged 47, since the age of 37 had complained of intermittent burning on urination and at times frequency and hematuria During the past 2 years he began to experience low abdominal pain radiating to both groins There were no other complaints, no previous illnesses and family and social histories were noncontributory Urinalysis revealed pyuria Blood urea nitrogen and alkali reserve were normal X ray studies by Dr Charles Charny revealed many large calculi overlying the sacrum There was a kidney shadow in the right loin and only a faint suggestion of a kidney on the left side After dye injection it was definitely ascertained that there was a pelvic kidney, but since there was no dye excretion on the left side, despite the suggestion of a left kidney shadow, Dr Charny made a provisional diagnosis of fused pelvic kidney Strengthening this opinion was the observation by x ray that large numbers of calculi were not segregated into secondary right and left conglomerations In the phenolsulphonphthalein test, dye appeared in 15 minutes

The patient was admitted to Mount Sinai Hospital on August 7, 1944 with the chief complaint of burning on urination Physical examination was essentially negative except for some slight tenderness in the lower abdomen and the presence of a large indirect reducible hernia on the right side Temperature was normal Urinalysis revealed 1–5 white blood cells and 30–35 red blood cells per high power

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The postoperative course appeared satisfactory for the first 6 days, except for the fact that the patient during this time exhibited psychotic tendencies (pulled out Wangensteen tube and intravenous needles, etc) His temperature fluctuated between 99 and 102 F with correspondingly rapid pulse and respirations Large quantities of urine (averaging approximately 75 ounces daily) drained through the nephrostomy tube Blood urea nitrogen determinations during this period were 23 and 28 6 mg per 100 cc of blood

On November 27, 1944 the output of urine decreased to 4 ounces in 12 hours, to which is to be added a 4 ounce drainage through the Wangensteen tube, the corresponding 12 hour intake had been 37 ounces That evening the patient became disoriented On November 28, 1944 at 1 30 a m , the intern was called to see the patient who had become violent, forced the restraining side gate and fallen to the floor Upon removing the dressings, a large portion of intestine was found eviscerated through the operative wound The exposed intestine was sprinkled with sulfanilamide powder and returned to the abdominal cavity and additional sulfanilamide powder sprinkled about the wound site The edges of the incision were then approximated by adhesive bands

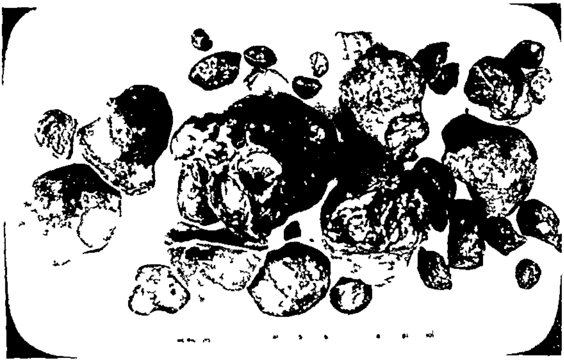

FIG 1 Photograph of facetted calculi removed at operation

From this time on the course was rapidly downhill Catheterization via urethra gave no return of urine The skin was cold and clammy, the pulse rapid and weak and the patient became semi comatose The temperature rose rapidly to 107 F (rectally) and the patient expired at 10 50 a m on November 28, 1944

The autopsy findings in the other organs are not of interest for our present purposes The adrenals were normal in size and position The anatomy of the kidneys was extremely unusual The two kidneys were completely fused to form one large disc shaped organ measuring 15 by 12 by 5 5 cm (fig 2) This fused kidney was located deep in the pelvis between the rectum and sacrum The peri renal fat was marked in amount A large mass of perirenal fat was found in the sac of the indirect inguinal hernia on the right side (observed clinically) What corresponded to the left renal artery had its origin at the bifurcation of the aorta

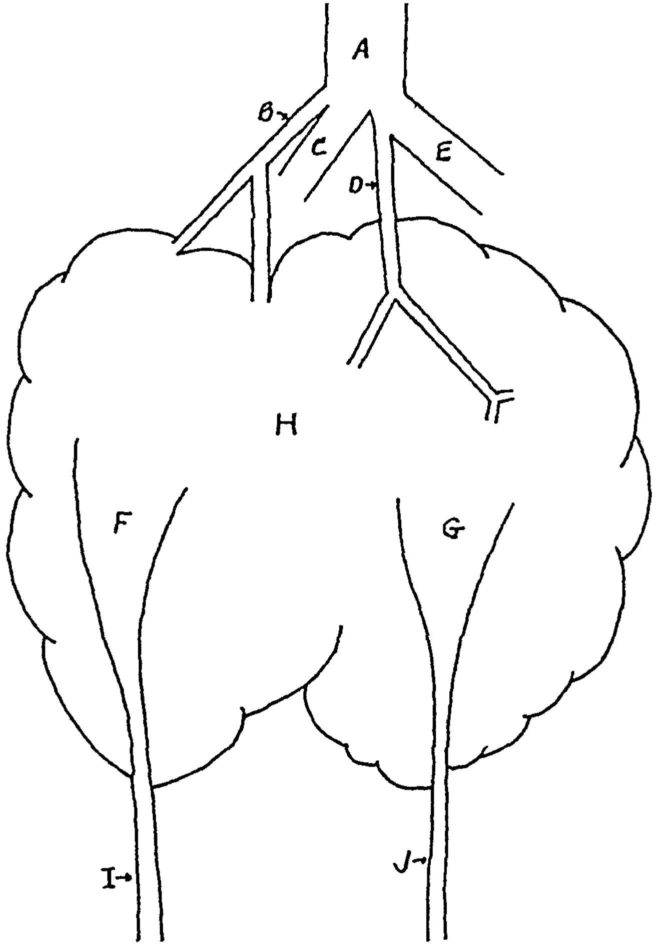

FIG. 2. Diagram showing completely fused kidneys. *A*, aorta; *B*, right renal artery; *C*, right iliac artery; *D*, left renal artery; *E*, left iliac artery; *F*, pelvis of right side of kidney; *G*, pelvis of left side of kidney; *H*, pelves intercommunicate inside kidney; *I*, right ureter; *J*, left ureter

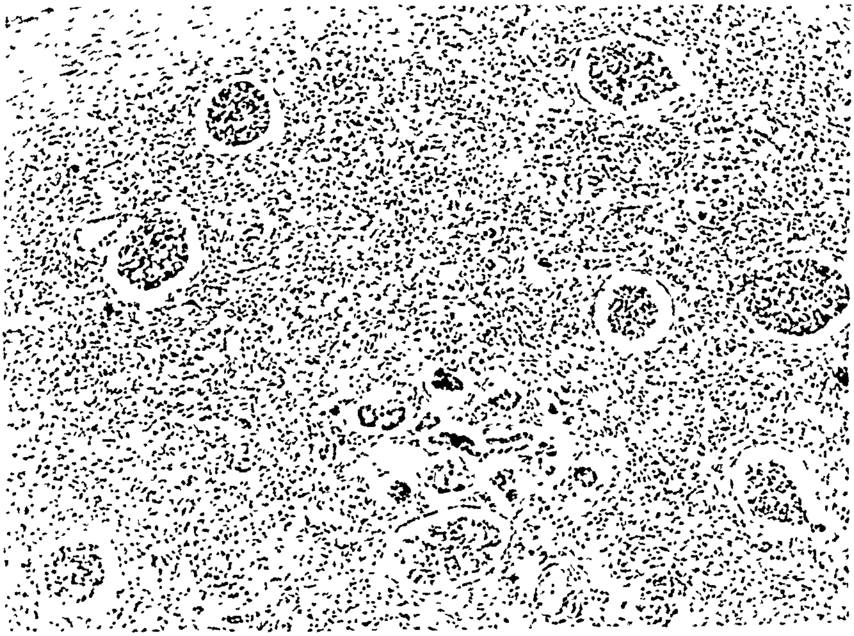

FIG. 3. Photomicrograph of left kidney, showing chronic pyelonephritis. × 70

The artery leading to the right side of the kidney mass originated just above the origin of the right iliac artery. The outer surface of the fused kidney was smooth and brown and presented occasional lobulations. One small simple cyst measuring 1 cm. in diameter was present at the upper pole on the right side. The kidney mass had been incised at operation on its anterior aspect to the right of the midline. On section, the entire left half of the fused kidney was found to consist merely of a thick, hollow shell whose wall measured 2–5 mm. This cavity contained several calculi, the largest measuring 2 by 2 by 1 cm. The inner surface of the cavity was smooth. The cut surface of the wall was yellowish-brown with markings resembling that of kidney cortex. The cut section of the right side presented the features of a normal kidney. The cortex was slightly widened and slightly pale. The medulla appeared congested. The cortico-medullary markings were indistinct. The vessels were not prominent. Two pelves and two ureters were present, one leading from the anterior aspect of each side of the fused organs. From the interior of the kidney it was seen that the two pelves intercommunicated. Both pelves were dilated, more so on the left side. The ureters reached the bladder at the normal sites of entrance. The left ureter measured 15 cm. in length and the right 25 cm. Both ureters contained numerous calculi and were dilated at the points where the larger calculi were located. The widest point in the left ureter measured 0.8 cm. and that in the right 1.0 cm. The bladder lay in normal position. It was small and empty. Its mucosa was smooth. The prostate was small. Its cut surface was greyish-white and slightly firm.

Microscopically, the left kidney showed a chronic, atrophic pyelonephritis (fig. 3); the right kidney showed marked cloudy swelling and marked congestion.

Death was attributed to shock and early uremia in a man with fused ectopic (pelvic) kidneys, the latter showing marked hydronephrosis and chronic atrophic pyelonephritis of the left kidney and moderate hydronephrosis of the right. In addition there was present marked bilateral hydro-ureters with a very large number of ureteral and pelvic calculi and a herniation of the perirenal fat of the right kidney through the inguinal canal on the right side.

DISCUSSION

J. Swift Joly in discussing "complete fusion" of the kidneys, describes the anatomy, which is similar to that seen in our case. In referring to the embryology, however, he states that "the clearest indication that these organs arise from the fusion of the two kidneys lies in the fact that they always have two renal pelves. They are situated on the anterior surface of the organ, at some distance from each other, and *never communicate.*" Our case, then, is perhaps unique in that here apparently the pelves do communicate.

Additional unusual features in this case are the hernia composed of perirenal fat and the very large number of renal calculi.

It is not unexpected that the adrenals were in their normal locations. Coppridge in discussing bilateral pelvic kidneys, states that in these cases the adrenals are usually found in the normal positions.

The fact that congenital anomalies occur more frequently in the kidney than in any other organ in the body may be attributed to the complex development of the urogenital apparatus. Excellent classifications of the anomalies of the kidney have been proposed. Abeshouse gives a convenient classification.

Reports in the literature affirm the fact that every congenital anomaly of the kidney is a potential clinico-pathologic entity. Some renal anomalies apparently exhibit a greater tendency to secondary disturbances than do others. The development of a disease process in the fusion and ectopic types of renal anomalies may be influenced by the blood supply, changes in form and position of the pelvis, and the course of the ureters. These anomalies and perhaps other factors apparently render the patient more susceptible to the development of urinary obstruction and stasis with resulting infection and calculosis (Abeshouse; Harris).

In reviewing the cases of bilateral renal ectopia observed clinically, the predominant symptom is found to be pain (Looney and Dodd). The pain varies from a deep-seated ache to intermittent attacks of acute sharp, stabbing colicky pains. "It is usually referred to the lower abdomen and suggests a low abdominal lesion involving the appendix, or the pelvic organs in the female. This symptom is, therefore, misleading and confusing from the standpoint of diagnosis. It is due to a lesion within the kidney or ureter itself, the most common being hydronephrosis, pyelonephritis and calculous disease" (Fowler). From the available evidence, however, the kidney anomaly of itself usually produces no symptoms; it is the secondary changes resulting from the anomaly that cause the pain and disturbances of urination.

The diagnosis of bilateral renal ectopia, in every recorded case diagnosed clinically, was made by pyelography. However, the anomaly is so rare that the condition is not usually suspected, and is rarely considered in the making of a differential diagnosis. There has been a definite increase in the number of anomalies diagnosed clinically. This is due largely to a wider appreciation of the value of a routine examination of the urinary tract in cases of abdominal pain which cannot be satisfactorily explained. In cases of ectopy, unilateral or bilateral, intravenous urography may give only suggestive results; exact details may be shown only by retrograde pyelography.

In our case an unusual problem in diagnosis presented itself. A diagnosis of renal anomaly with secondary disturbances had been established. The question naturally arose at the time of the patient's last admission as to whether the pain in the right lower quadrant and the accompanying signs and symptoms could be definitely explained on the basis of the anomaly or whether there was present a superimposed acute appendicitis. Because of the presence of signs and symptoms characteristic of acute appendicitis and because of the possible danger of delay, the decision to operate appeared to have been a reasonable one. Realizing that the kidney might still be the source of trouble, an extraperitoneal incision was made. The history in this case emphasizes once again how closely the picture of acute appendicitis may be simulated by renal ectopia and its resulting complications.

It is not within the scope of this presentation to discuss the treatment of this type of anomaly. Each case must be handled as an individual problem in this regard. Fowler points out that bilateral ectopic kidneys function normally and may continue to do so throughout life, the condition then being recognized only at the autopsy or dissecting table. The discovery of a "cake" kidney in a 70 year old man by Looney and Dodd illustrates this point. In general, the treatment, when necessary, is similar to that employed in kidneys in normal position. The surgical treatment of the congenital anomalous kidney is comprehensively discussed by Abeshouse.

CONCLUSION

The literature on the extremely rare congenital anomaly, completely fused pelvic kidney, is reviewed. An additional case is presented and is of particular interest because of the unusual associated clinical manifestations, and in having been diagnosed clinically. The case is unique in that the pelves in the fused kidney communicate.

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TROCAR NEPHROSTOMY

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Trocar nephrostomy is an emergency procedure in cases in which the patient is in a very poor condition.

Nephrostomy is mostly a rather makeshift palliative procedure, because the patient's condition does not permit any corrective or curative measures. And yet its mortality is high, in spite of the fact that our primary aim in performing nephrostomy is to restore kidney drainage immediately, and temporarily tide over an extremely ill patient.

There is a difference between the so-called classical and trocar nephrostomy. Both procedures can be used in emergencies. Whichever classical method is applied, the mobilization of the kidney with the pelvic approach inflicts an additional stress to an already weakened system. The classical method should be used only as a preliminary or supportive measure for other surgical procedures. The trocar nephrostomy, with its minimal operative interference, should be used only in emergencies, with the aim of lessening high mortality rate.

The aim of an ideal nephrostomy should be:

1) Performance in the shortest time with a simple but accurate technique.
2) Minimum trauma:
   a) No kidney mobilization.
   b) Retroperitoneal structures should not be disturbed.
3) The best possible kidney drainage should be achieved.
4) The convalescent period should be uneventful, with no urinary sinus, or fistula formation.
5) The kidney pelvic mucosa should not be damaged to prevent any serious increase of infection.
6) If it becomes necessary to replace a tube or catheter, it should be done with as little difficulty as possible.

The indications for a trocar nephrostomy are:

1) Anuria following surgical procedures, where the result of an additional operative risk is doubtful. This may occur after bilateral ureteral postoperative damage from:
   a) Injuries causing a severed ureter or removal of a large segment of a ureter.
   b) Ligation, usually after a hysterectomy, where ureteral deligation is either hazardous or impossible.
   c) Edema following electrocoagulation or radiation in cases of urinary tract tumors or after ureteral instrumental manipulation. This may occur after catheterization, or after appendectomy, pelvic abscess or postoperative periureteral adhesions.
2) Anuria, due to a solitary kidney (either a congenital one or where one kidney was previously removed) or where one kidney is extensively destroyed

from any pathological cause. This may be due to:

   a) Reflex anuria, as after bilateral ureteral catheterization.
   b) Hydro-uretero-pyonephrosis with or without calculus, or a congenital one.
   c) Bilateral nephrolithiasis.
   d) Impassable inflammatory strictures of the ureter.
   e) Surgical nephritis, after severe kidney injuries or rupture.
   f) Ureteral obstructions due to tuberculosis, or malignant diseases, or peridiverticulitis.

3) Anuria, with uremic signs in an acute medical nephritis with a fulminating infection, which does not respond to conservative treatment. In cases of pressure uremia, partial decapsulation is indicated for relief of tension and conservation of renal parenchyma. The obstruction in a pressure uremia may be detritus of tubular epithelial or blood cells, crystals, certain types of casts which dilate kidney tubules, inducing an interstitial edema with inflammatory exudate and swelling of the tubular epithelial cells.

   These may be due to:

   a) Poisoning, as from mercurials, arsenicals, phenol, sulfonilamides, cantharides.
   b) Acute diseases, as typhoid fever, scarlet fever, pneumonia, etc.

4) In severe pyelitis of pregnancy, complicated with profound toxemia and an extremely poor condition.

TECHNIQUE OF TROCAR NEPHROSTOMY

The patient is placed, after proper preoperative care, prone on the table, arms upward. Cushion pads are placed bilaterally in front under the kidney, without tension. Regional or local anesthesia is preferable because of the poor condition of the patient. The twelfth rib is defined by palpation and its direction traced on the skin. A wheal is raised paravertebrally under the twelfth rib and another wheal above the crista ilei. Between these two wheals the paravertebral muscles are infiltrated with 60 cc of $\frac{1}{2}$ per cent novocaine solution to block the dorsal nerve trunks, so that the D.VIII, D.IX, D.X, D.XI and D.XII nerves are interrupted. The skin is also infiltrated subcutaneously along the intended incision with 20 cc of $\frac{1}{2}$ per cent novocaine solution. The operator stands on the left side of the patient for the left kidney, on the right side for the right kidney.

The skin incisions are shown in figure 1. As the iliocostal space is only slightly widened, due to the patient's position, one may use:

a) A longitudinal incision from the outer edge of the sacrospinal muscle and just below the last rib on downward, extending to between the middle of the space of the rib and ileac crest. This skin incision is similar to the original Simon's incision.
b) Or one may use a 5–6 cm. long vertical incision from the outer edge of the sacrospinal towards the anterior axillary line parallel to the last rib.

The incision is deepened until the muscles are reached, retracting the subcutaneous tissues. With a hemostat the muscles are pierced roughly. The left index finger is put along it. The muscles are separated, forcibly stripping their undersurface from the lumbodorsal fascia. Retracting the muscles, the dorsolumbar fascia is visible and perforated with a forceps in the line of its fibers and the index fingers pushed through it. The fascia of Gerota or Zuckerkandl is stripped from under the surface of the lumbodorsal fascia and if peritoneum is present, it is pushed gently forwards. On the left kidney the posterior layer of the Gerota's or Zuckerkandl fascia is separated with the spread right index and middle fingers and pressing with the back of these fingers the quadratus lumborum and psoas muscles, the lower pole of the kidney is freely exposed. The kidney is left in situ and not delivered or displaced or damaged by traction or pressure. Due to the limited space, following the muscle splitting, this is not possible anyway. The posterior-inferior surface of the left kidney is palpated with the right index and middle fingers and the left kidney pelvis is localized posteriorly by palpation. If it is necessary to locate it we may press the ureter and trace it upwards to the pelvis. With the point of the trocar the kidney capsule is nicked 1 cm. posterior to the convex border of the lower pole of the kidney, which is steadied with the right index and middle fingers. If a partial decapsulation is warranted at this stage, it can be performed. The trocar and its cannula are thrust through this small incision into the parenchyma of the kidney, possibly through the lower calyx, parallel to the right index and middle fingers, whose tips are on the kidney pelvis. The trocar and its cannula are pushed into the kidney until the tip of the right index finger does not feel the sharp point of the trocar in the kidney pelvis (fig. 2, *A*). While the tube or cannula is held securely in the kidney pelvis, the trocar is removed. A prepared lubricated catheter is held taut by a straight stylet and inserted through this tube into the pelvis, until it is palpated well beyond the end of the tube. The catheter is steadied in the pelvis and the stylet withdrawn when the wings of the catheter are unfolded and palpated in the pelvis. Making tractions on the catheter with the tip of the index finger toward the pelvis the trocar tube is now pulled out leaving the catheter in the pelvis. (fig. 2, *B*). The catheter can now be connected with a syringe or suction apparatus, and if the operation is successful, the first drop of urine is visible. As the catheter acts as a hemostat with its pressure on the kidney tissue, usually there is not much bleeding, otherwise, hemostatic gauze can be used around it. After we are convinced that the cathe-

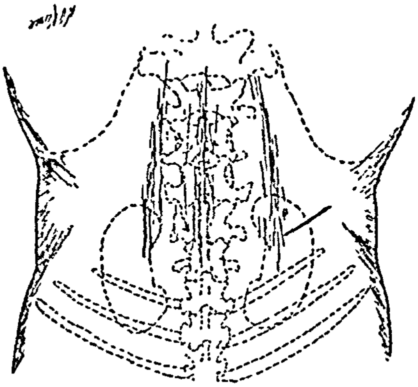

Fig. 1

ter in the kidney is straight and not tortuous, and after replacing the Gerota's or Zuckerkandl's fascia, the renal capsule is sutured with plain catgut to the lumbodorsal fascia. The lumbodorsal fascia is sutured with chromic catgut. After placing a Penrose drain the muscles fall together, thus requiring no sutures. The catheter is fastened to the skin after the subcutaneous and skin approximation.

There may be a sharp organic reaction until the patient becomes accustomed to the free drainage. Therefore it is advisable to give abundant fluids, and maintain an acid urine to avoid incrustations. If it is necessary to change catheters, the patient should also be in an identical operative position thus facilitating a straight line, when inserting it.

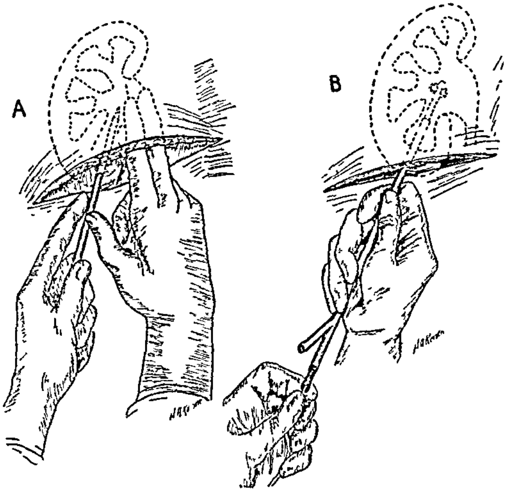

Fig. 2

CASE ABSTRACTS

Case B2525 was a middle aged woman suffering from anuria after hysterectomy for multiple and interligamental fibromyoma. As ureteral catheters were not passable on the second postoperative day, trocar nephrostomy was performed. One week after the operation ureteral cathereters were passed and kidney function restored.

Case B9194 was an elderly man who developed anuria, probably due to ureteral edema following an unsuccessful cystoscopic manipulation for removing a calculus from one ureter. Due to an impacted calculus catheter passage was not possible in the other ureter. One week after bilateral trocar nephrostomy a catheter was passed.

Case C1665 was an elderly woman who developed anuria due to ureteral stricture and periureteral infiltration following radiation for carcinoma of the cervix.

Two weeks after bilateral trocar nephrostomy, the patient, who was in an absolutely poor condition, succumbed due to metastatic pneumonia.

COMMENT

a) Advantages

Draining the kidney by means of trocar nephrostomy and a self-retaining catheter seems to be advantageous for the following reasons:

As the trocar is introduced in the avascular zone of Hyrtl-Broder, hemorrhage and leakage around the catheter should be, at least in theory, minimal. Although the kidney in anuria is usually enlarged, red, and shows an extremely nephritic pattern, the congestion makes the organ extremely hyperemic and therefore bleeds profusely. The resulting infarcts in it are smaller after the operation.

The kidneys remain in situ; they are not delivered. As the upper pole of the kidney is not touched, blood vessels are not torn, the kidney remains fixed, bound down by its fascia. Even if the kidney is bound down due to diffuse perirenal inflammations, this does not interfere with the easy approach to our operative field, the inferior pole of the kidney.

We may orientate ourselves about the eventual anomalies of the ureter and the form of the pelvis, if we follow the course of the ureter to the kidney with our finger tips. Despite the opinion of Hyrtl that no two kidney pelves are alike, we classify their form, according to Papin, as: 1) the textbook variety; 2) the enlarged; 3) the bifurcated or trifurcated; 4) the branching; 5) the very small; 6) the very large; 7) those with a horizontal axis; 8) those with a vertical axis; 9) those with a contracted neck; 10) the angulated; 11) those with a bifid ureter.

As the kidney is not changed from its original position, because it is not luxated, the inserted drainage tube is therefore straight and not subjected to any angulation. The tube may be replaced with little difficulty and with more accuracy if it is necessary. As the catheter tube is placed into the pelvis through the lower calyx, the kidney is drained from its most dependent portion, assuring an adequate drainage. An adequate drainage and a clean nephrostomy tube led Albarran to the conclusion that the kidneys are almost immune to any damage due to a nephrostomy tube.

b) Disadvantages

Objections to a cortical approach of the kidney pelvis are:

Where the kidney parenchyma is thick and the pelvis is relatively small.

Where the soft and friable kidney cortex is readily penetrated with a blunt instrument, but its pelvis is quite resistant. This may deflect the instrument along the side of the pelvis, making its drainage difficult. Sometimes even palpation of the region of the hilus may cause one to believe that the cavity of the pelvis is entered, when actually it is not.

The small drainage tube may obstruct the infundibulum, thereby causing the minor calyces to be blocked, and stone formation may occur.

SUMMARY

Bilateral trocar nephrostomy is advocated as an easy emergency measure to tide over patients, where extensive surgery would be absolutely contraindicated. The technique of trocar nephrostomy is described.

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LIPOSARCOMA OF THE KIDNEY: REPORT OF AN EARLY CASE

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This tumor of the kidney appears to be a rare lesion. From the scarcity of reports in the literature, and to the best of our knowledge, only 12 cases have been previously reported. This is the fifth case in which an individual was not suffering from the tuberous sclerosis complex.

These tumors appear in two different types of patients. The first group is seen in individuals suffering from tuberous sclerosis and adenoma sebaceum (Pringle) of the face. Seven such cases have been described: 4 by Fischer, and 1 each by Fish and McLaughlin, Froug and Harbitz. This is a peculiar finding and difficult to explain. The other group, including our patient, were in individuals who had liposarcoma of the kidney unassociated with this complex. These were reported by Hartwig, Judd and Donald, McCartney and Wynne, and Tesler and Koiransky. Most of the reported cases have been in patients in whom the renal tumor has been massive and the main complaints have been referable to a palpable tumor in the abdomen. In the following case the kidney did not seem enlarged, nor was a mass felt.

CASE REPORT

A white man, aged 37 years, was admitted to this hospital on December 4, 1947, with a complaint of 2 days' duration. This consisted of a general onset of pain in the right posterior hip region, along the posterior crest of the ilium and the right costovertebral area. The pain was knife-like in character, excruciating, coming at irregular intervals, lasting 30 minutes at a time, and the patient stated he was unable to walk or sleep. These symptoms began while the patient was riding a motor car in a coal mine where he was employed. There was no recent history of trauma. The patient remembered having had blood in the urine for several days when he was a child. At the age of 12 he couldn't pass urine for 2 days, but the symptoms disappeared spontaneously.

The physical examination was essentially negative, except for the presence of severe tenderness in the regions mentioned above. Pain was elicited on flexing the right lower extremity on the abdomen. The blood pressure was 140/90.

The red blood count and hemoglobin were in the normal range. White blood count was 15,000 per cu. mm. with 77 per cent segmenters. Urinalysis revealed a slight trace of albumin, many red blood cells and a few white blood cells. An excretory urogram showed a marked defect of the right renal pelvis which appeared to be secondary to a tumor in the region of the renal pelvis. This had resulted in only a slight dilatation of the calyces. The excretion time was normal. Bilateral retrograde pyelograms showed a tumor or cyst of the right kidney. X-ray of the chest showed no pathological change.

Nephrectomy was performed through a loin incision in the usual manner, under cyclopropane anesthesia. The renal pedicle was not involved. The postoperative condition was uneventful and the patient was discharged from the hospital on the eleventh postoperative day.

The gross specimen consisted of a right kidney which measured 15 by 9 by 6 cm. and weighed 260 gm. It was semifirm in consistency and the capsule stripped with ease, leaving a purple-gray smooth surface. The cortex measured 7 mm. in thickness, was purple-gray and the markings were distinct. The medulla was purple-red and was replaced in its middle one-third by a circumscribed, partially encapsulated tumor node. The tumor measured 5 by 5 by 4 cm. and extended to the hilum. It was soft to semifirm in consistency and, on section, was yellow-gray, granular and necrotic. Few islands of normal adipose tissue were seen in the center of the tumor. The lumens of the renal pelvis and calyces were narrowed and their mucosa was pink-gray and smooth. The renal vein was patent.

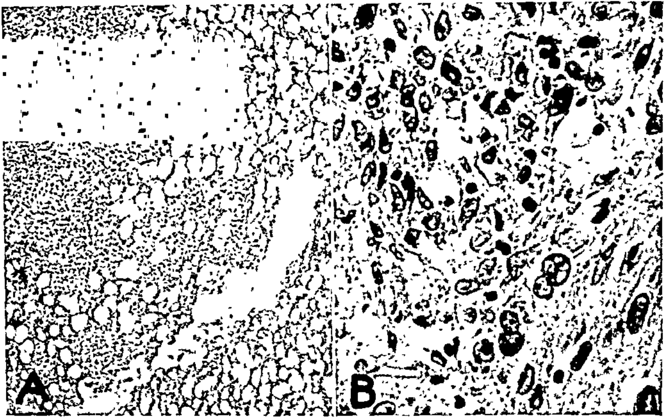

FIG. 1. *A*, low power photomicrograph of adipose tissue with islands of sarcoma. *B*, high power photomicrograph of vacuolated liposarcoma cells.

Microscopic examination of the tumor showed areas composed largely of adult adipose tissue which contained small to large cellular islands of cells varying in size and shape (fig. 1, *A*). Many of the cells were spherical to polyhedral, with round to oval vesicular nuclei and their cytoplasm contained vacuoles (fig. 1, *B*). Sudan III stains were positive for fat. There were round and spindle shaped cells present, arranged in sheets. Their cytoplasm contained no vacuoles. Mitotic figures were occasionally seen. The microscopic picture was interpreted as being of a liposarcoma and intermediary differentiation type and of a low grade malignancy.

The patient has been symptom free for the past 8 months and apparently has had no recurrence of the tumor or evidence of metastasis.

DISCUSSION

Most of the cases of liposarcoma of the kidney previously reported were huge tumors and far advanced at the time they came to operation or autopsy. The histogenesis of this tumor resolves itself in origin from the lipoblast, which is a specialized fat forming mesenchymal cell. Stout, in his report, has shown interesting observations on these tumors in general. They show a great variation in their growth rate, some rapid, and others slow. Metastasis is less common than in other types of sarcoma. It is difficult to say whether liposarcomas develop from preexisting lipomas. The large majority are probably malignant from the beginning.

Prognosis of liposarcoma varies since these tumors can be classified from their histology as the well differentiated myxoid type, poorly differentiated myxoid type, round cell or adenoid type and mixed groups. The first type offers the best prognosis since they remain in the state of good differentiation and rarely ever metastasize. In our case, the histopathology was that of the first type.

SUMMARY

A case of an early liposarcoma of the kidney is presented. It is the fifth case unassociated with the tuberous sclerosis complex. Liposarcomas are rare and peculiar tumors and prognosis is variable.

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WILMS' TUMOR: A REVIEW OF FIVE YEAR SURVIVALS IN THE LITERATURE AND REPORT OF TWO CASES

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From the Charity Hospital of Louisiana, New Orleans

In the out-patient department of this hospital we have been following a little Negro girl who had a Wilms' tumor. Recently she passed the 5 year survival period which has been more or less arbitrarily fixed as the period necessary to indicate a cure in most malignancies, and this fact stimulated our interest in the subject of Wilms' tumors, especially in regard to treatment and results. A review of the literature and a review of all cases of Wilms' tumor diagnosed in this hospital in the 10 year period since July 1937 was made.

A critical review of the literature revealed that although many hundreds of Wilms' tumors have been diagnosed, there are very few 5 year survivals. In their exhaustive review of the literature covering 383 cases in 1938, McNeill and Chilko found reports of 10 cases in which the patients survived 5 or more years. However, further analysis of these 10 cases reveals 1 case reported by Hyman to be a hypernephroma; the case reported by Mac Kenzie to be actually the same case as reported elsewhere by Kretschmer; and the 2 cases reported by Mixter as being subsequently included in the reports of Ladd and White. In 1938 Kretschmer reported 3 survivals out of 24 operated cases, only one of which had survived 5 years. Three years later, in 1941, Ladd and White reported 14 "probable" cures out of 60 cases, and 8 of these cases had lived 5 or more years. In that same year Higgins and Shively added 4 more 5 year cures to the literature out of a series of 26 cases. In 1943 Ockerblad and Carlson reported one 5 year survival and Priestley et al. reported 7 survivals out of 44 cases treated at the Mayo Clinic. Of these, 5 patients had lived for from 5 to 20 years. In 1945 Mandeville and Nelson added the report of one 5 year survival, and the following year Deming in a review of all the renal tumors seen in the New Haven Hospitals in 23 years reported one 5 year survival. To the above cases Nesbit and Adams in 1946 added the report of 8 survivals out of 16 cases treated at the University of Michigan Hospital. Six of these cases had survived more than 5 years. This gives a total of 33 proven cases of Wilms' tumor which have survived for 5 or more years. Other cases reported as cures which had survived for 2, 3, or 4 years have not been included in this series.

In reviewing the literature one gains the impression that some authors believe that survival of a case of Wilms' tumor for 1 or 2 years after treatment justifies considering the case as cured. While it certainly is true that most patients who have recurrence of their tumor do so quickly and die within the first year, it has been shown on many occasions that patients may survive over 2 years and subsequently die of recurrence and metastasis. Two of the patients in our series here at Charity Hospital lived 29 months and died of tumor recurrence. The most outstanding example is Abbe's patient who lived 4 years and 9 months and died of metastasis. No patient has been reported to die of the disease after surviving

5 years. These facts emphasize the need for prolonged observation of these cases before considering them cured.

The treatment of Wilms' tumors is by one of five methods: 1) nephrectomy alone; 2) preoperative radiation and nephrectomy; 3) nephrectomy and postoperative radiation; 4) preoperative radiation, nephrectomy, and postoperative radiation; and 5) radiation alone. No sufficiently large group of cases has been treated by one method to give good comparative values of the various types of therapy. In nearly all cases nephrectomy has been performed, and the total number of survivals has been highest in the group that has received nephrectomy alone. This does not indicate, however, that radiation therapy is not of value, and in the hands of many surgeons preoperative x-ray has been found to so reduce the size of a large tumor as to render surgery possible on a case previously considered inoperable. Nesbit even reports 1 case of a 10 year survival after radiation alone. This child, a hydrocephalic, had a positive diagnosis made by punch biopsy and was living and apparently free of tumor 10 years after a course of deep x-ray therapy. This is the only reported case of a 5 year cure by radiation alone in which a definite pathological diagnosis was made. As Dean so aptly states the case, there is no clear cut method of treatment applicable to all cases, and the best treatment in any given case depends on the following variable factors: 1) the condition of the patient; 2) the ability of the surgeon; and 3) the availability of good x-ray therapy.

TABLE 1.—*Wilms' tumor: Five year survivals*

AUTHOR	NUMBER OF CASES	METHOD OF TREATMENT				
		Nephrectomy alone	Nephrectomy pre-op. x-ray	Nephrectomy post op. x-ray	Nephrectomy pre-op. x-ray postop. x-ray	X-ray alone
Abbe	1	1				
Coley	1	1*				
Deming	1	1				
Higgins and Shively	4	2	1		1	
Kretschmer	1			1		
Ladd and White	8	8†				
Mandeville and Nelson	1		1			
Nesbit and Adams	6	2	2	1		1
Ockerblad and Carlson	1			1		
Priestley et al.	5	1		2	2	
Wade	1	1				
White	1	1				
Wallstein	2	2				
Authors' cases	2			1	1	
Totals	35	20	4	6	4	1

* The case reported by Coley was operated on by Dr. J. W. Perkins and subsequently received Coley's vaccine.

† One of Ladd's cases which is a 5 year survival or a probable survival received preoperative x-ray.

An attempt has been made in table 1 to show each case of Wilms' tumor proven by histological study which is known to have survived for 5 or more years, and to indicate in each case the method of treatment To the 33 cases reported in the literature are added 2 additional cases reported by the authors

During the 10 year period from July 1, 1937 to June 30, 1947 there were admitted to the Charity Hospital of Louisiana at New Orleans a total of 521,147 cases Of these there were 15 cases of Wilms' tumor Five of these cases were treated by preoperative radiation, nephrectomy, and postoperative radiation, 2 by preoperative radiation and nephrectomy, 5 by nephrectomy and postoperative radiation, 1 by nephrectomy alone, and 2 by radiation alone In the 2 cases treated by radiation alone, the diagnosis was confirmed in 1 case by exploration and biopsy, and in the other by autopsy

Of the 15 cases treated, 12 are now dead, 11 dead of Wilms' tumor Fourteen of the cases were operated upon and there was one surgical mortality Of the 11 patients who died because of Wilms' tumor, eight succumbed during the first year, one during the second year, and two during the third year The remaining patient who died survived 46 months and died after a brief illness in another hospital The diagnosis was diphtheria and the patient might have survived the 5 year period had she not fallen victim to this intercurrent illness The 3 remaining patients are alive and well with no evidence of tumor recurrence at the end of 74, 65 and 9 months respectively Of course the 9-month survival is too short to be of any significance The 2 patients who survived over 5 years are reported more fully below

CASE REPORTS

Case 1 A M S (L41-20594), a 7 months old Negro baby, was admitted May 2, 1941 with a chief complaint of grossly bloody urine and high fever of 1 week's duration The mother had also noticed a mass in the left side of the abdomen The past medical history was essentially negative On physical examination the patient appeared to be acutely ill The findings were normal except for a large visable and palpable mass on the left side of the abdomen This mass was firm and bulged into the lumbar space, it was thought to be a renal tumor Excretory urograms and retrograde pyelograms were both unsatisfactory, x rays of the chest and long bones revealed no evidence of metatasis Urine cultures were negative Without preoperative radiation, the patient underwent a left nephrectomy on May 23, 1941 (by Dr H T Beacham) without difficulty through a lumbar incision She had an uneventful recovery, and was given deep x-ray therapy postoperatively Microscopic pathologic diagnosis "Kidney, Wilms' tumor" (fig 1)

When last seen in the clinic July 11, 1947 (six years and 2 months postoperatively) the patient was well and there was no evidence of recurrence of the tumor

Case 2 J R (Tul 42 53197), a Negress 2 years of age, was admitted to the hospital because of a mass in her left abdomen which the mother had first noticed one day previously There had been no symptoms associated with this mass, but the mother remarked that for 2 days the child's feet were slightly swollen so that it was difficult to put on her shoes Review of systems and past medical history were negative On physical examination the only finding of significance was the large, firm, nontender mass which occupied the entire left abdomen and lumbar region from the costal margin to the level of the anterior superior iliac spine. There was a suggestion of edema of both ankles.

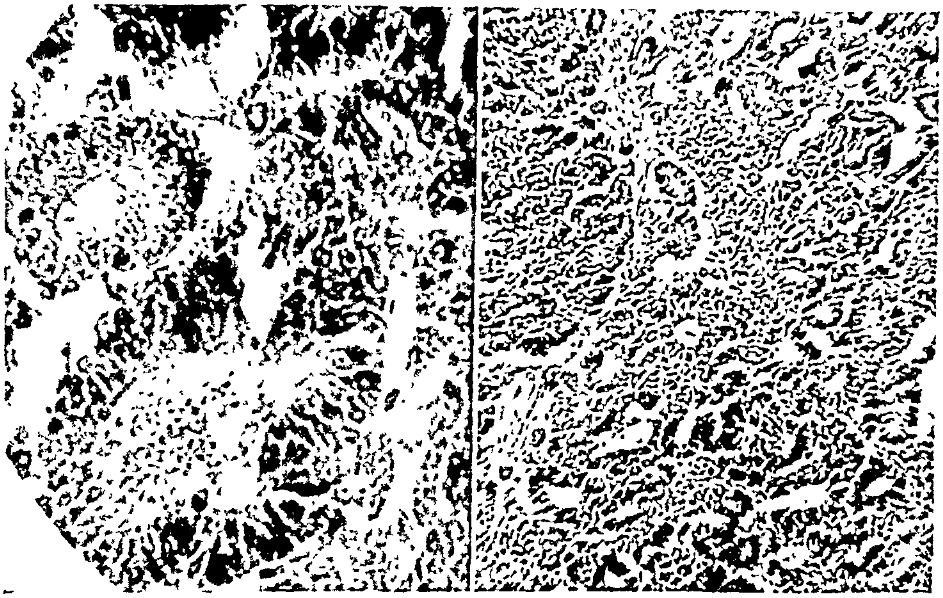

FIG. 1. Low and high power photomicrographs, showing sarcomatous appearance of tumor with many attempts at tubule formation.

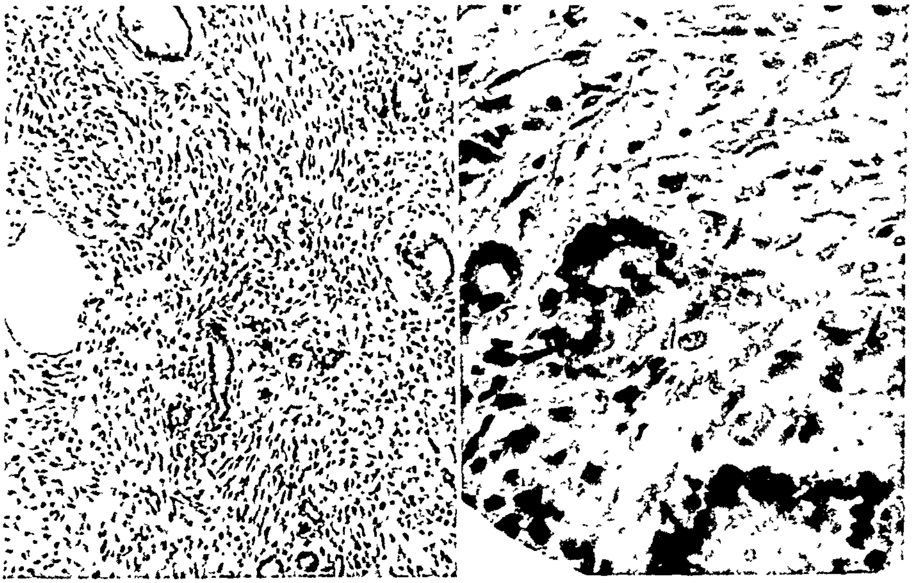

FIG. 2. Low and high power photomicrographs, showing sarcomatous appearance of tumor with scattered tubules.

Intravenous and retrograde pyelograms were interpreted as revealing a large intrinsic renal tumor on the left side. The right kidney was entirely normal.

A diagnosis of Wilms' tumor was made. Because of the large size of the tumor, deep x-ray therapy was given 12 days but had to be discontinued because the patient developed nausea, vomiting, fever and leukopenia. Ten days after the x-ray therapy was discontinued, a left nephrectomy was done (by Dr. J. D. Mitchell) through the usual lumbar incision without difficulty. The patient had an uneventful recovery and went home on the fourteenth postoperative day. She received postoperative deep x-ray therapy.

Microscopic pathologic diagnosis: "Wilms' tumor (rather large cystic structures are prominent)". See figure 2.

When seen in the clinic in December 1947, the patient was doing well and there was no evidence of recurrence of the tumor. At that time, 5½ years had elapsed since the diagnosis of Wilms' tumor was first made.

SUMMARY

The findings of a thorough review of the literature on Wilms' tumor are presented, with emphasis placed on the methods of treatment and the number of 5 year survivals. These data are presented in table form. In addition, the 15 cases of Wilms' tumor diagnosed in the Charity Hospital of Louisiana from 1937 through 1947 are briefly discussed and the 2 patients who have survived five or more years are presented as case reports.

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THE CLINICAL USE OF URECHOLINE IN DYSFUNCTIONS OF THE BLADDER

PRELIMINARY REPORT

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Urecholine (the urethane of beta-methylcholine chloride; also known as carbaminoyl-beta-methylcholine) is one of a group of choline esters that act primarily as stimulants of the parasympathetic nervous system. When administered in therapeutic dosages orally or subcutaneously there is little or no effect upon the heart rate, blood pressure or peripheral circulation of normal human subjects. It is known that the drug increases peristalsis and stimulates micturition.

Starr and Ferguson (1940) suggested the use of urecholine in postoperative urinary retention and Winter (1941), using a cystometrographic technique on unanesthetized dogs, showed that urecholine lowered the vesical capacity and increased the irritability of the bladder.

Urologists are often confronted with chronic urinary retention from hypotonic dysfunctions of the bladder without any evidence of mechanical vesical neck or urethral obstruction. There are also certain instances in which one is justified in feeling that vesical neck obstruction has been adequately removed by prostatectomy or other surgery, yet the patient continues to carry residual urine. These situations may occur in patients who have a central nervous system lesion or a weakened detrusor muscle. It was with the thought in mind that perhaps urecholine might be of value under these circumstances that observations regarding the effect of the drug upon the human bladder were begun.

METHOD

Observations were made to determine:

1) Effect of urecholine on the normal human bladder.

2) Effect of urecholine on the human bladder exhibiting chronic hypotonic dysfunction.

3) Effect of urecholine on acute postoperative urinary retention in humans.

The immediate effect on the normal bladder and the bladder with chronic hypotonic dysfunction was determined by cystometrographic studies. Cystometry is a method for determining and graphically recording the functional activity of a bladder at any given time. Many types of cystometers have been described. Essentially such an apparatus must consist of a calibrated burette to supply water, and a manometer attached by a connecting tube to a bladder catheter. By reason of compactness and accuracy, the apparatus using a Tycos aneroid manometer head (fig. 1) is most useful. During the examination water should be allowed to flow into the bladder at a rate not greater than 90 drops per minute. Intravesical pressure is determined at increments of 50 to 100 cc of water. The curve obtained is determined by the detrusor tonus. Other per-

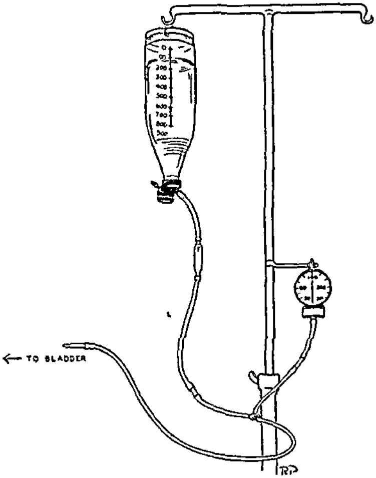
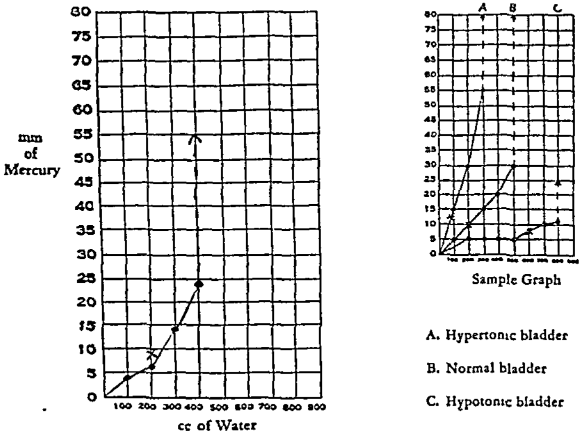


FIG. 1. Cystometer



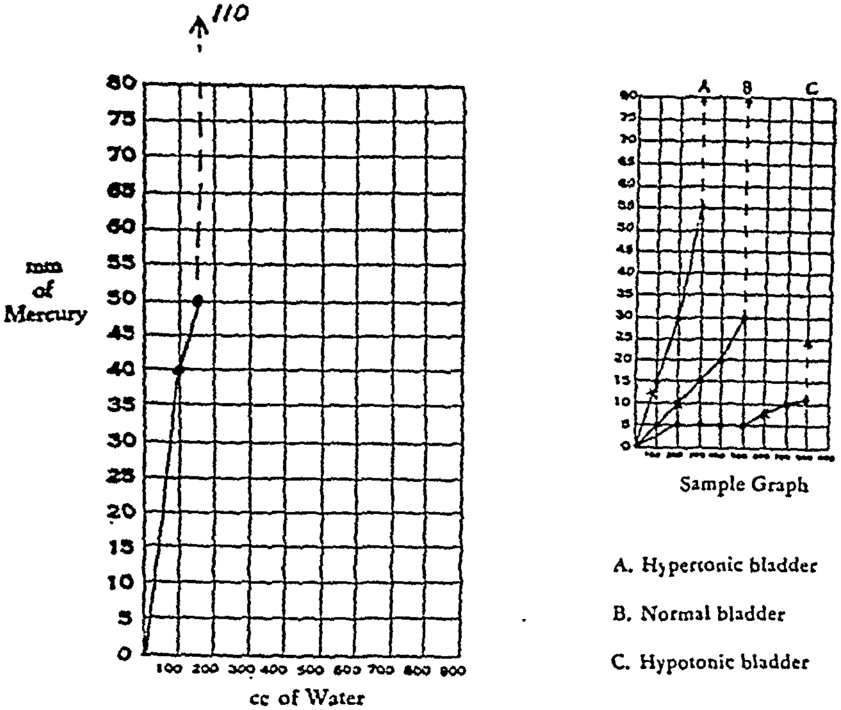
FACTORS

Data Obtained	Normal	Hypertonic	Hypotonic
First desire to void 200 cc.	150-250 cc	Under 100 cc.	Above 250 cc.
Maximal pressure 25 mm.	Gradual	Acute	Flat
Maximal Voluntary pressure 55 mm.	60-80 mm	Over 90 mm.	Under 40 mm.

FIG. 2. Cystometrographic characteristics of normal bladder before administration of urecholine.

tinent information obtained on cystometrographic examination includes the following: 1) volume of water in the bladder when the patient has the first desire to void; 2) maximum volume that patient can hold and pressure at this volume; 3) maximum voluntary pressure when patient has a full bladder.

The characteristics of the normal average bladder are: First desire to void: 150 to 250 cc. Capacity (without painful distension): 350 to 450 cc. Maximum voluntary pressure: 60 to 80 mm. of mercury. Gradual increments in intravesical pressure curve. Residual urine: none. Micturition reflex initiated by intravesical pressure of 11 to 13 mm. of mercury.



FACTORS

Data Obtained	Normal	Hypertonic	Hypotonic
First desire to void.........75..................cc.	150-250 cc.	Under 100 cc.	Above 250 cc.
Maximal pressure..............50..............mm.	Gradual	Acute	Flat
Maximal Voluntary pressure......110......mm.	60-80 mm.	Over 90 mm.	Under 40 mm.

FIG. 3. Cystometrographic characteristics found in normal bladder 5 minutes after subcutaneous administration of urecholine, 5 mg.

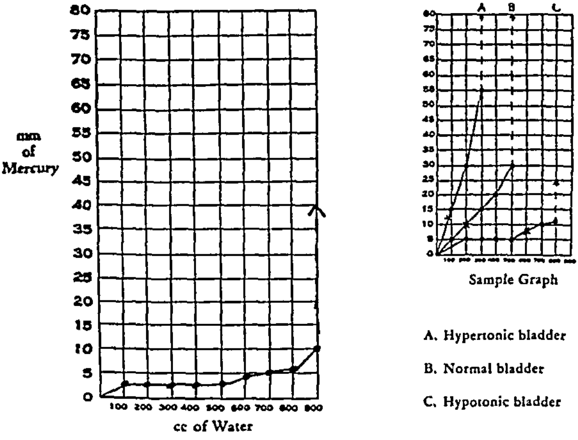
On the basis of cystometrographic observations one may identify normal neuromuscular relationships, hypertonia, and hypotonia.

The cystometrographic characteristics of a normal bladder before administration of urecholine are shown in figure 2, while figure 3 gives the findings on the same bladder 5 minutes after the subcutaneous injection of 5 mg. of urecholine. It may be seen that vesical capacity is reduced, the tonus of the detrusor increased, and the maximum voluntary voiding pressure increased. Observations showing the effect of urecholine on several normal bladders are shown in table 1. These findings are all similar to the graphic presentation in figure 1.

TABLE 1.—*Effect of urecholine* on normal bladder*

OBSERVATION NUMBER	BEFORE URECHOLINE				AFTER URECHOLINE				
	1st desire to void	Vesical capacity	Maximum pressure	Maximum voluntary pressure	Time after Urecholine	1st desire to void	Vesical capacity	Maximum pressure	Maximum voluntary pressure
	cc	*cc*	*mm. Hg*	*mm. Hg*	*min.*	*cc*	*cc*	*mm. Hg*	*mm. Hg*
1	200	400	25	55	5	75	150	50	110
2	200	400	25	55	60	150	200	50	90
3	250	500	20	60	10	150	300	30	70
4	200	500	20	50	5	100	150	35	80
5	200	600	20	90	10	50	300	40	110

* The amount of urecholine given in each instance was 5 mg. subcutaneously.



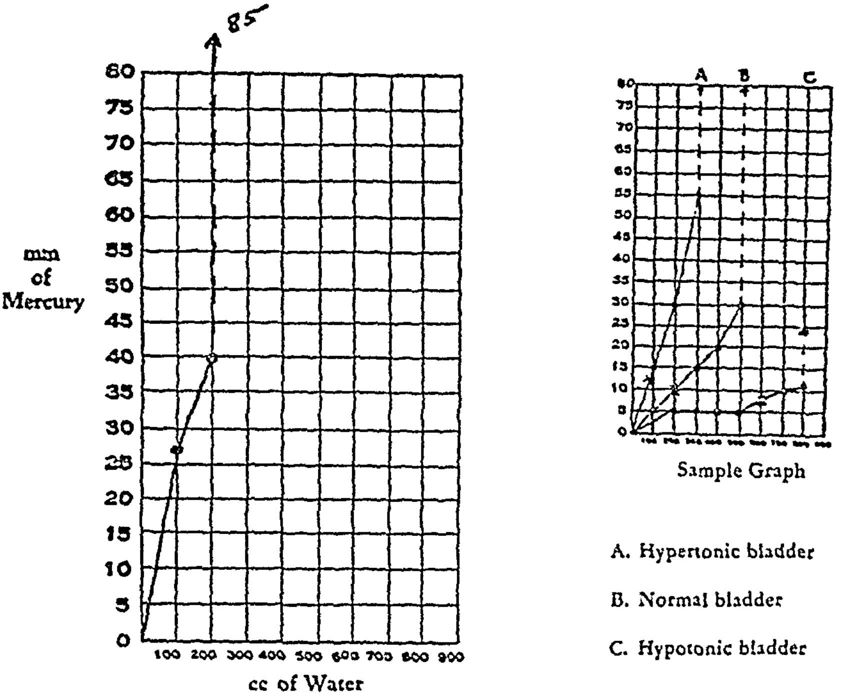
FACTORS

Data Obtained		Normal	Hypertonic	Hypotonic
First desire to void 500	cc.	150-250 cc.	Under 100 cc	Above 250 cc.
Maximal pressure 10	mm.	Gradual	Acute	Flat
Maximal Voluntary pressure 40	mm.	60-80 mm.	Over 90 mm.	Under 40 mm.

FIG. 4. Cystometrographic characteristics of bladder of patient with chronic hypotonic dysfunction before urecholine.

Figure 4 shows the cystometrographic characteristics of the bladder of a patient with chronic hypotonic dysfunction. This patient had a myelitis involving the cauda equina area. Figure 5 shows the findings in the same bladder 5 minutes after subcutaneous injection of 5 mg. of urecholine. A marked decrease in vesical capacity, increase in vesical tonus, and increase in maximal voluntary voiding pressure are evident. Observations of cystometrographic findings upon several patients with hypotonic dysfunction of the bladder are presented in table 2.

The clinical effect of urecholine upon acute postoperative urinary retention, reported first by Starr and Ferguson, and corroborated by personal observations shown in table 3, suggested the possible effect of urecholine upon chronic hypotonic dysfunction of the bladder.



FACTORS

Data Obtained	Normal	Hypertonic	Hypotonic
First desire to void ......100............. cc.	150-250 cc.	Under 100 cc.	Above 250 cc.
Maximal pressure . 40 ....mm.	Gradual	Acute	Flat
Maximal Voluntary pressure...85.........mm.	60-80 mm.	Over 90 mm.	Under 40 mm.

Fig 5. Cystometrographic characteristics of bladder of patient with chronic dysfunction 5 minutes after subcutaneous administration of urecholine, 5 mg.

Observations upon patients with bladders showing evidence of chronic hypotonic dysfunction, from variable etiology, are presented in table 4. Particular attention is directed to the marked and almost uniform drop in the amount of residual urine following urecholine medication. This is to be viewed of both experimental physiological significance and of clinical importance.

DISCUSSION

These observations indicate a powerful effect of urecholine on the normal bladder, the bladder showing acute postoperative urinary retention, and the bladder showing chronic hypotonic dysfunction from various forms of primary etiology.

Although the drug is not effective in every instance, it would appear that it answers the need for an effective agent, free from severe side reactions, to decrease vesical capacity, increase vesical tone and contractility, and reduce residual urine in certain patients with chronic hypotonic dysfunction of the bladder.

The following methods of management are suggested.

1) For chronic hypotonic dysfunction of the bladder: Urecholine 10 to 20 mg. orally every 6 to 8 hours. (The drug has been continued daily for as long as 3 months without evidence of harmful effect.) Test for residual urine every 2 to 4 days until base line is reached.

2) For acute postoperative urinary retention: Urecholine 10 to 20 mg. orally or 5 mg. subcutaneously. Repeat dosage if patient does not void within 30 minutes. Catheterize if second dose is not successful.

TABLE 2.—*Effect of urecholine* on the hypotonic bladder*

OBSERVATION NUMBER	BEFORE URECHOLINE				AFTER URECHOLINE				
	1st desire to void	Vesical capacity	Maximum pressure	Maximum voluntary pressure	Time after urecholine	1st desire to void	Vesical capacity	Maximum pressure	Maximum voluntary pressure
	cc	*cc*	*mm Hg*	*mm Hg*	*min*	*cc*	*cc*	*mm Hg*	*mm Hg*
1	300	500	15	40	5	150	500	30	80
2	300	500	15	40	20	100	250	25	75
3	500	900	10	40	5	100	200	40	85
4	500	900	10	40	30	250	500	40	90
5	350	700	10	40	5	300	700	15	60
6	350	700	10	40	60	200	500	30	70
7	350	700	10	40	90	350	600	20	60
8	300	800	20	40	10	150	500	20	70
9	300	800	20	40	90	300	600	20	50
10	300	600	5	10	5	80	500	20	65
11	400	500	15	30	5	100	300	30	80
12	400	500	15	30	150	300	450	20	80
13	700	700	15	30	10	450	600	20	60
14	550	800	5	15	10	125	500	20	50
15	550	800	5	15	60	400	800	15	40
16	450	800	10	25	10	125	600	20	90

* The amount of urecholine given in each instance was 5 mg. subcutaneously

There are definite contraindications to the use of urecholine. Intramuscular or intravenous administration should be avoided as certain severe reactions may occur, characterized by such symptoms as headache, sweating, circulatory collapse, drop in blood pressure, abdominal cramps, diarrhea, shock, and in some instances bronchoconstriction. The antidote for such reactions is atropine. Urecholine should not be given to patients with a history or evidence of mechanical vesical neck or urethral obstruction. It is proper to rule out such possibilities by history and cystoscopic examination before beginning therapy.

CONCLUSIONS

The particular field of usefulness of this drug, in the light of our present knowledge, lies in the management of acute postoperative urinary retention and chronic

TABLE 3.—*Clinical use of urecholine* in acute postoperative urinary retention*

PATIENT NUMBER	AGE	SEX	FOLLOWING	TIME INTERVAL BEFORE URINATION	AMOUNT VOIDED
				min.	*cc*
1	32	male	Hemorrhoidectomy	20	500
2	19	male	Nephrectomy	15	500
3	20	male	Orchidopexy	10	800
4	43	male	Nephrectomy	10	600
5	31	male	Appendectomy	30	450
6	56	male	Nephrectomy	15	500
7	60	male	Gastric resection	15	650
8	61	male	Cholecystectomy	12	540
9	63	male	Leg amputation	20	300
10	61	male	Cholecystectomy	10	250

* Patient #1 received urecholine 2 mg. orally, #8 and #10, 10 mg. subcutaneously, and all others 5 mg. subcutaneously.

TABLE 4.—*Clinical use of urecholine in hypotonic dysfunctions of the bladder*

PATIENT NUMBER	AGE	SEX	DIAGNOSIS	DOSAGE OF URECHOLINE	TOTAL DAYS URECHOLINE GIVEN	RESIDUAL URINE BEFORE URECHOLINE	RESIDUAL URINE AFTER URECHOLINE
				mg.		*cc*	*cc*
1	49	male	Post-transurethral resection atony	10 qid	2	390	100
2	69	male	Arteriosclerosis of spinal cord	10 qid	4	300	50
3	39	female	Trauma of spinal cord	2 qid	10	180	0
4	74	male	Taboparesis	10 tid	10	700	75
5	70	male	Arteriosclerosis of spinal cord	5 tid	2	165	0
6	78	female	Arteriosclerosis of spinal cord	2 tid	11	750	0
7	70	male	Arteriosclerosis of spinal cord	2 tid	12	300	90
8	54	male	Herniated disc Cord pressure	5 tid	30	350	15
9	22	female	Postpartum retention	2 tid	18	400	0
10	32	female	Postpartum retention	2 tid	30	500	0
11	59	female	Chronic retention after cystocele repair	5 tid	5	200	10
12	43	male	Herniated disc Postoperative laminectomy	5 tid	20	120	15
13	66	male	Spinal cord tumor Postoperative laminectomy	10 qid	9	350	25
14	68	female	Arteriosclerosis of spinal cord	10 tid	10	800	200
15	72	male	Post-transurethral resection atony	10 tid	4	150	0

hypotonic dysfunction of the bladder resulting from various forms of primary etiology.

For obvious reasons the drug is contraindicated in the presence of vesical neck obstruction due to mechanical causes

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CYSTITIS: CLASSIFICATION AND TREATMENT; DISCUSSION OF TYPE OCCURRING AFTER TRANSURETHRAL RESECTION[1]

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Cystitis or inflammation of the bladder is due to infection by the various micro-organisms that invade this viscus. Through the ages cystitis has been the subject of many articles. Early publications were based on clinical studies alone, and it remained for Guyon and his students to clarify this disease by making studies based on scientific investigation. Little has been added to the subject since the publication of the classical article in 1902 by Hallé and Motz, who accurately reported the pathologic bladder changes due to cystitis. In 1921 Heitz-Boyer presented an exhaustive study of acute and chronic cystitis. In 1937 Deming reviewed the etiological causes in 1,317 cases of cystitis, clarifying more recent concepts.

Acute cystitis may be due to infection arising from the kidneys above, or caused by invasion via the urethra from below. Clinically, cystitis is characterized by the classical symptoms recognized since the beginning of medicine. These consist of frequent urination, dysuria, passage of cloudy, foul urine and terminal hematuria. Usually acute cystitis is of short duration, particularly since the advent of sulfa therapy and the powerful antiobotics penicillin and streptomycin. Chronic cystitis may be secondary to various lesions of the kidney and to those of the bladder itself, viz., stone formation, cancer, trophic disturbances, syphilis, presence of foreign bodies, etc. It may also be due to extrinsic causes: perivesical adhesions following surgical intervention on the neighboring structures such as the genital organs in women, appendicitis, diverticulitis, etc.; to radium therapy, sclerosis of the fibro-adipose tissue making up the serous coat of the bladder, etc. Often it is secondary to obstructive lesions of the vesical neck such as hypertrophy of the prostate, median bar formation, polypi, cysts, etc. Sometimes it follows transurethral resection of the prostate, regional resection of the bladder for cancer, fulguration of benign and malignant papilloma.

In this paper we will discuss the prevention and treatment of the new form of cystitis following endoscopic prostatic resection. Frequently it accompanies urethral stricture, skenitis and cystocele. In some cases chronic cystitis demands treatment of underlying kidney lesions such as tuberculosis, pyonephrosis, calculous formation, etc.; in others it calls for the correction of the intrinsic and extrinsic lesions of the bladder itself as well as those of the prostate and urethra.

For clarification a comprehensive classification is proposed with the desire to aid in the diagnosis and treatment of all types of cystitis.

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[1] Official paper of delegate of American Urological Association, delivered before the Third American and Fourth Brazilian Urological Congress, Rio de Janeiro, Brazil, Sept. 17, 1947.

ACUTE CYSTITIS

Acute cystitis is of short duration, lasting less than 10 days Usually it is due to invasion by gonococci, colon bacilli or staphylococci by way of the urethra These cases clear up immediately after the administration of the sulfonamides, penicillin or streptomycin An interesting form of cystitis is that of the newlywed in which trauma due to coitus unquestionably plays a dominant role Those cases accompanying skenitis, prostatitis, seminal vesiculitis and pyelonephritis readily respond to treatment directed to the organs in which acute inflammation has taken place and includes, among other measures, the administration of urinary antiseptics, the sulfas and the more recent antibiotics A rare form is due to the secondary manifestations of syphilis and herpes zoster The former rapidly responds to antisyphilitic treatment and the latter disappears in a manner similar to the clinical course of herpes zoster elsewhere in the body In more recent years an interesting form of cystitis has been observed to follow transurethral resection of the prostate, electrical regional resection of the bladder for cancer and fulguration of bladder polypi, papilloma and cancerous growths In most cases the reaction taking place in the bladder brought about by electrical removal of tissue, whether by cutting current or electrocoagulation, lasts from 3 to 8 weeks In some cases cystitis occurs after transurethral resection in which removal of the infected prostate is not complete, and inflammation of the bladder along with its debilitating symptoms may become chronic In recent years it has been our practice to remove, by enucleation, all infected hypertrophied prostates weighing 30 gms and over, in order to prevent debilitating chronic secondary infection of the bladder

CHRONIC CYSTITIS SECONDARY TO KIDNEY LESIONS

Chronic cystitis, not due to intrinsic or extrinsic bladder lesions, is invariably caused by infectious disease of the kidneys In all of these cases one should proceed to make a complete investigation of the kidneys, including bacteriologic studies, renal function tests, pyelography, etc The most common lesions encountered are pyelonephritis, sclerosing and otherwise, infectious calculous disease of the kidney and ureter, pyonephrosis, tuberculosis and urethral stricture In dealing with tuberculous cystitis persisting after removal of the unilateral tuberculous kidney, we call attention to the importance of the management of the nephrectomized patient This includes routine postoperative cystoscopic examination by virtue of which treatment of remaining ulcers of the bladder can successfully be carried out and strictures of intramural portion of the remaining ureter relieved In tuberculous patients, on whom this follow up care was carried out, a higher survival rate was noted than in those who had no postoperative treatment Streptomycin is an added weapon in the treatment of residual urinary tract infection in the form of cystitis in the patient nephrectomized for renal tuberculosis It offers some hope in the amelioration of suffering due to bilateral tuberculosis of the kidneys Its curative value, however, is highly problematical We have noted recurrence of tubercle bacilli in the urine after massive treatment with streptomycin

CHRONIC CYSTITIS DUE TO INTRINSIC BLADDER LESIONS

Cystitis due to the presence of single or multiple stones has long been recognized. In the early days of urology they were readily detected by the characteristic sound transmitted in passing the exploratory metal sound or catheter; more recently the diagnosis is accurately made by x-ray and cystoscopic examination. Cystitis readily clears after removal of the offending stone. However, obstructive lesions of the vesical neck, including median bar formation and hypertrophy of the prostate which are often contributing factors in its formation, should be corrected by transurethral resection or prostatectomy. In cases presenting stones in an infected diverticulum, one should carry out diverticulectomy.

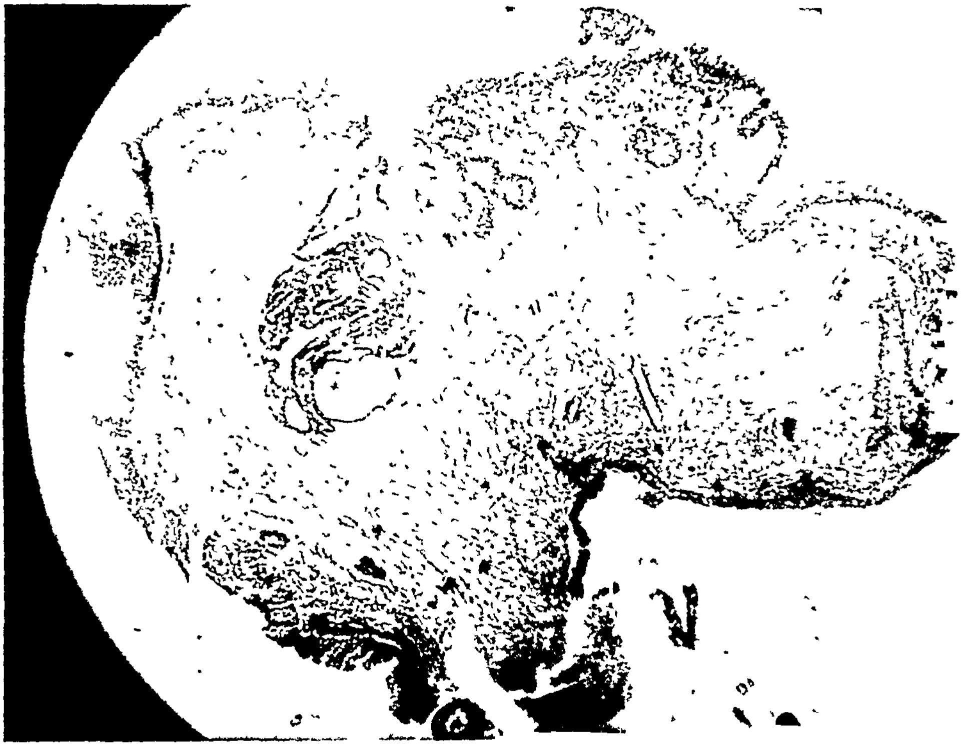

Fig. 1 Photomicrograph (Leitz oc. 1, ob. 3) of infected polypus of vesical neck. Removal of this polypus and fulguration of base were followed by relief of chronic cystitis.

I recall an interesting case of cystitis due to a stone consisting of calculous deposits on a piece of shrapnel which had made its way into the bladder from the adjacent soft tissue of the bony pelvis. In dealing with this veteran of World War I, we elected to remove the stone by cystotomy rather than lithotripsy to the great satisfaction of all concerned!

We have noted many cases of cystitis secondary to polypi (fig. 1), small cysts and infected glands of the bladder neck and posterior urethra. These are due to infection of the mucous glands, occur quite commonly in women and are often secondary to infectious lesions of the kidney. In men they are commonly due to infection of the prostate and seminal vesicles as well as of the kidney. Cystitis often accompanied benign and malignant papilloma of the bladder as well as carcinoma. See figures 2 and 3. In these, hematuria is a predominant symptom, and in cases in which no macroscopic blood has been observed, invariably one encounters microscopic blood cells in the urine.

In recent years, interstitial cystitis, otherwise known as submucous fibrosis, frequently accompanied by ulcer formation, has challenged the ingenuity of the urologist. The condition was accurately described by Hunner in 1914, and the ulcer that bears his name also has been called submucous ulcer, panmural ulcer, etc. This trophic disturbance of the bladder, characterized by painful frequent urination and hematuria, has been treated by irrigation of the bladder with silver nitrate, instillation of the various dyes and hydraulic distention of the bladder (Moore) under anesthesia, along with measures taken to eliminate foci infection elsewhere in the body and the administration of vitamin therapy. The ulcer is best treated by fulguration (surgical excision, quite popular a few years back, is now rarely employed). In some cases fibrosis and contraction of the bladder progress to such an extent that the viscus is literally closed and the resulting suffering demands ureterocutaneous or uretero-intestinal anastomosis.

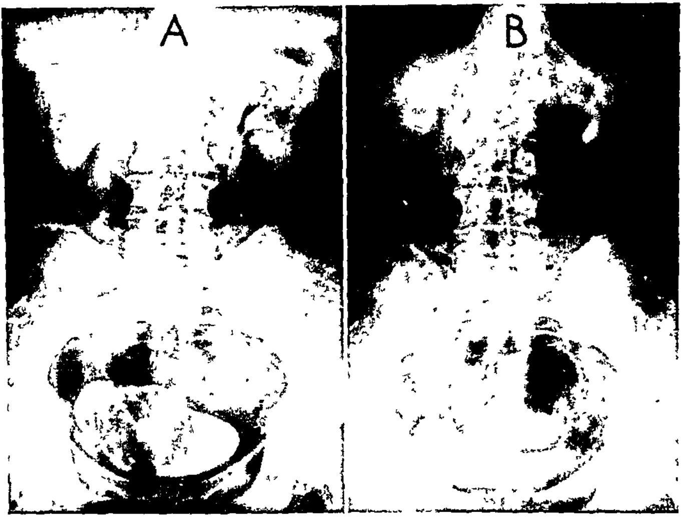

FIG. 2 *A*, cystogram, demonstrating large benign papilloma of bladder. *B*, cystogram taken after electrical excision through open bladder. Chronic cystitis relieved after removal of bladder tumor

Cystitis due to cystocele has long been recognized and is easily remedied by surgical correction of the cystocele. The type due to radium burn, following radiation therapy of malignant tumors of the cervix, is resistant to treatment. In these, fibrosis of the tissue making up the bladder wall and adjacent structures plays a dominant role. Cystitis accompanying neurogenic disease is more common in cases in which urinary retention is present. Catheter drainage and immobilization favors alkaline type of infection. The spastic obstructing hypertrophied vesical neck, causing obstruction, is successfully relieved by transurethral resection. During the past year we have relieved two women, suffering from marked cystitis, by endoscopic excision of the obstructing neurogenic bladder neck. In these patients residual urine consisted of 750 and 1500 cc respectively.

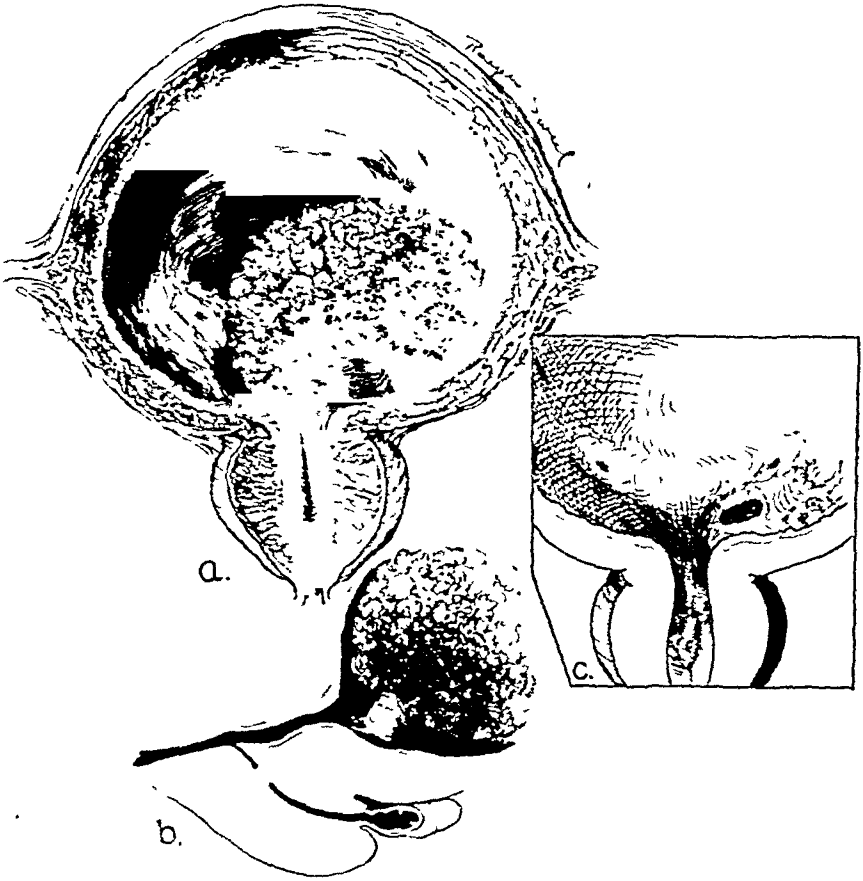

FIG. 3.*a*, Drawing of pedunculated papilloma in base of bladder. *b*, Sagittal section. *c*, Cystoscopic appearance of bladder 6 months after destruction by fulguration. In spite of removal of papilloma, cystitis persisted.

Of interest are the relatively rare forms consisting of alkaline encrusted cystitis, cystic as well as emphysematous, pseudomembranous and the vegetative types. In the alkaline type it is necessary to carry out acidification of the urine by the administration of mandelic acid and an acid ash diet. In some cases it is necessary to remove the encrustations by cystoscopic maneuvers and to carry out continuous irrigation of the bladder with mild acid solutions such as phosphoric acid 1:1000, acetic acid 1:2000 and solution G.

EXTRINSIC BLADDER LESIONS

Cystitis is often due to distortion of the bladder resulting from operations on neighboring organs, particularly interventions on the uterus and ovaries. We have encountered a number of such cases in which cystoscopic examination revealed invagination of the bladder by pressure from without, due to including the bladder wall in a suture or to fibrosis resulting from healing. It is commonly caused by pressure of the prolapsed or gravid uterus or adjacent pelvic tumors such as fibromyomata, ovarian cysts, etc. We observed an interesting case in which a ptosed kidney had fallen so low that it exerted actual pressure on the bladder; producing debilitating symptoms over a period of 9 years (fig. 4). Nephropexy promptly relieved the patient of cystitis. It has been observed to accompany lesions of the gastro-intestinal tract such as colitis, appendicitis, diverticulitis, etc. In some cases diverticulitis is followed by suppuration, and perforation of the bladder takes place, resulting in the formation of a vesico-intestinal fistula. I recall a woman who suffered from cystitis due to such a fistula. The adjacent infected bowel was resected, the severed ends approximated by an end-to-end anastomosis and the fistulous opening in the bladder wall resected. This was followed by complete relief of bladder symptoms. A similar fistula was seen in a man, aged 76, in whom the risk was too great to permit carrying out this radical operation. He survived 5 years.

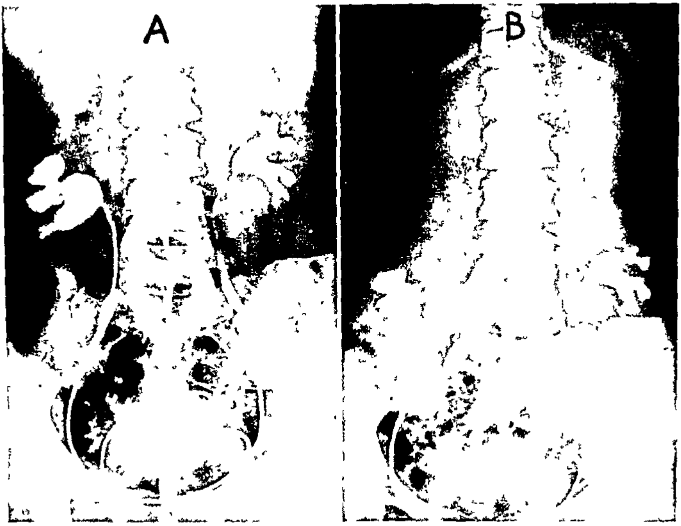

FIG. 4 *A*, retrograde pyelogram of patient who suffered from pain in right abdomen and cystitis. Note low position of right kidney and dilatation of pelvis. *B*, retrograde pyelogram taken in vertical position, showing marked torsion and ptosis of right kidney exerting pressure on bladder. Nephropexy and detorsion of right kidney relieved cystitis of 9 years' duration.

Chronic cystitis is sometimes due to osteomyelitis of the bones making up the pelvic girdle, and is likely to follow fracture of the pelvis and rupture of the bladder. In 1940 we reported 3 such cases. In one, relief was finally attained by the removal of an infected sequestrum, measuring 3 cm. in diameter, associated with the os pubis. Up to that date the literature revealed very little on the clinical entity of chronic cystitis resulting from traumatic and hematogenous osteomyelitis of the pelvic girdle associated with sequestra, abscess formation, osteovesical fistula and urinary calculi. In some cases cystitis is due to fibrosis of the adipocellular tissue associated with the serous coat of the bladder. This form of pericystitis is quite resistant to treatment. We have encountered such a case in performing suprapubic prostatectomy. In distending the bladder with water under anesthesia in order to facilitate exposure, not more than 100 cc could be made to enter this contracted viscus. In opening the bladder marked sclerosis was noted in the adipocellular tissue of the prevesical space.

Chronic cystitis often accompanied chronic prostatitis and seminal vesiculitis. It is necessary to clear up the infection of the prostate and seminal vesicles by massage and stripping, as well as utilizing vaccine therapy and administering the more recent urinary antiseptics including the sulfas and antibiotics. Certain cases of prostatitis present concomitant cysts and polypi of the bladder neck and posterior urethra. In 1921 we called attention to the role such inflammatory tumors play in keeping infection in the prostate and bladder. Such cases of cystitis and prostatitis will not clear up until these small infected tumors are eradicated by fulguration. Some instances of chronic cystitis present residual infected urine in the bladder due to stasis caused by median bar formation and varying degrees of prostatic enlargement. These obstructive lesions of the bladder neck must be removed by endoscopic resection or prostatectomy. Strictures of the urethra and ejaculatory ducts should be treated by dilatation in order to establish adequate drainage.

Another form of chronic cystitis has come into being since the advent of transurethral resection as a popular method for relieving stasis due to prostatic hypertrophy. It is generally conceded that, in spite of the pretentions of the most enthusiastic resectionists, it is almost impossible to entirely remove the larger types of prostatic hypertrophy by transurethral resection. In many instances remaining infected prostatic tissue is responsible for chronic cystitis characterized by frequent, painful urination and recurrent hematuria. There is no question that in many instances cystitis is due to faulty technique: the resection was incomplete, and the remaining nodules of prostatic tissue, that have been overlooked, act as a source of chronic irritation and infection. We share the opinion of many urologists, viz., the larger adenomas of the prostate are best treated by surgical enucleation. By removal of the entire prostate there is less likelihood of encountering the unpleasant complication of persistent chronic cystitis which commonly occurs when endoscopic resection is employed for the relief of these larger hypertrophies.

Chronic cystitis due to urethral lesions will respond to treatment if the underlying disease of the urethra is corrected. Throughout the ages urologists have stressed this point. Urethral stricture must be relieved by progressive dilatation with sounds or by internal urethrotomy. Stones must be removed by open operation or cystourethroscopic maneuvers. In a patient presenting all the classical symptoms of chronic cystitis, advanced stricture was suspected, but examination revealed a large impacted oval-shaped stone (2 cm by 4 cm) in the prostatic urethra Bladder symptoms subsided after the removal of the calculus by perineal resection Occasionally urethral diverticulum occurs and is a source of chronic irritation to the bladder until it is removed Chronic infection of the glands of Littré, usually a late complication of gonorrhea, tends to prolong cystitis By means of endoscopy they are easily detected and destroyed by electrocoagulation

The disabling complication of urethrorectal perineal fistula, which may follow perineal prostatectomy is also a source of chronic infection of the bladder Over the years I have encountered 5 such cases, 1 on our service, and 4 in consultation They were subjected to repeated operations surgical repair, colostomy, diversion of the urinary stream by cystotomy, and nephrectomy for the removal of a kidney destroyed by ascending infection Two of these patients were relieved by virtue of these corrective operations, the other three are still disabled invalids Because of the likelihood of this embarrassing complication we have abandoned the perineal route for the removal of benign adenoma, preferring to employ the suprapubic operation which we have perfected and simplified We reserve the perineal approach for radical prostatectomy in early cancer Inflammation of the bladder quickly disappears after removal of the fistulous communicating tract

CONCLUSIONS

An etiological classification of acute and chronic cystitis is presented

Acute cystitis, secondary to inflammatory lesions in the urethra, prostate, seminal vesicle, cervix, kidney, etc , readily responds to sulfa therapy and the administration of penicillin and streptomycin Attention is called to the form of acute cystitis that follows transurethral resection of the prostate

Chronic cystitis is often secondary to kidney lesions and in many instances is due to intrinsic and extrinsic diseases of the bladder

New concepts of treatment are presented for tuberculous cystitis persisting after nephrectomy for renal tuberculosis Postoperative management consists of periodic cystoscopic examination and includes fulguration of bladder ulcers and dilatation of the intramural portion of the remaining ureter Streptomycin is an added weapon in the treatment of residual tuberculous cystitis as well as for the type secondary to bilateral renal tuberculosis It gives great amelioration of symptoms, however, its curative value is problematical

Interstitial cystitis, at times accompanied by Hunner's ulcer, still taxes the ingenuity of the urologist despite treatment consisting of fulguration, resection, bladder irrigation with silver nitrate, instillation of the various dyes, hydraulic distention under anesthesia, elimination of focal infection and vitamin therapy In some instances we are still obliged to have recourse to uretero cutaneous or uretero intestinal anastomosis

The clinical entity is presented of chronic cystitis resulting from traumatic and hematogenous osteomyelitis of the pelvic girdle associated with sequestra, abscess formation, osteovesical fistula, and urinary calculi

Discussed in detail is a new form of chronic cystitis occurring after transurethral resection for prostatic hypertrophy. Often it follows incomplete resection, and is more likely to occur when the endoscopic operation is carried out on the larger types of prostatic adenoma which are best treated by surgical enucleation.

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PRIMARY LYMPHOSARCOMA OF THE URINARY BLADDER[1]

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Lymphosarcoma of the urinary bladder is a rare disease, only 6 authentic cases having been reported in the literature

In 1885 Eve cited a male patient 68 years of age, in whom the right lateral wall of the bladder was involved by the tumor

Chaffey reported a case in 1885 of a boy 3 years of age in whom a lymphosarcoma of the bladder was a postmortem observation

In 1927 Maragna presented a report of a male patient 37 years of age The tumor was excised by suprapubic cystotomy

Dupont and Misrachi in 1931 described a case of a woman 32 years of age Two tumors of the bladder were removed by resection, the microscopic study demonstrating lymphosarcoma

The fifth case was described by Kreutzmann in 1942 This was a woman 47 years of age in whom the tumor was removed by segmental resection

In 1944 Rathbun and Wehrbein reported a case of a woman 64 years of age with multiple bladder tumors They stated "A complete resection was impossible without transplanting the right ureter and the general condition of the patient excluded such an extensive procedure" The tumors were excised with a loop and the base of the tumors thoroughly fulgurated with the coagulating current

CASE REPORT

A white unmarried girl 20 years of age was observed in the Department of Urology February 3, 1937, complaining of pain in the lower mid-abdomen dating back to childhood For 1 year she had been aware of mild frequency of urination, nocturia 2 to 3 times and occasional dysuria She had been studied previously at the age of 11 years because of pain in the lower abdomen of 1 year's duration This discomfort presented itself at intervals of 2 weeks and was localized medial to the left anterior superior spine, the attacks awakening her at night or a seizure occurring during the day The pain was not associated with changes in the bowel habits and not accompanied by nausea or vomiting Physical examination revealed no abnormal findings and a definite diagnosis was not established On a recent visit she stated that the lower abdominal discomfort had continued and a dull aching pain was constantly present, varying in severity and intensity. This was aggravated during the menses or with strenuous exercise

She had observed increasing frequency of urination, and nocturia 5 to 7 times No history of hematuria was elicited There was no radiation of the pain She stated that albumin had been present in the urine for 10 years with an increase in the amount during the past 6 months There had been no loss in weight during the present illness

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[1] Read at annual meeting, North Central Section, American Urological Association, Des Moines, Iowa, October 28, 1948

The family history was irrelevant and the patient gave a history of an appendectomy, performed in 1934. The physical examination revealed a well developed and well nourished girl, 20 years of age. The blood pressure was 120/80. The examinations of the head and neck showed normal findings. The lungs were clear to auscultation and percussion. The heart was not enlarged and no murmurs were audible nor irregularities detected.

The abdominal examination revealed a well healed low midline scar. There were no organs or masses palpable, but suprapubic tenderness was elicited on palpation. The extremities and reflexes were normal. There were no masses or tenderness present on rectal examination.

The reaction of the urine was acid, albumin 2 plus, sugar 0; on microscopic study an occasional red blood cell and numerous white blood cells were observed. The culture yielded B. coli. Upon blood examination the hemoglobin was 84 per cent, red cells 4,590,000, white cells 8,500. The blood sugar was 72 mg. per 100 cc of blood, urea 27 mg. and the Wassermann was negative. The initial roentgenogram showed the kidneys normal in size, shape and position.

The intravenous urogram showed prompt function of both kidneys (fig. 1). There was reduplication of the right ureter in the upper half. The total function appeared normal. The cystogram presented a filling defect involving the left side of the bladder.

Cystoscopic survey revealed a grade 1 cystitis. There was a large mass protruding into the bladder. The mass involved the left wall of the bladder and in close proximity to the left ureteral orifice. The mucosa was intact over the tumor and no ulceration was observed. It was my impression that this was a large extravesical mass encroaching on the bladder.

An exploratory operation was performed on February 18, 1937. At this time a large mass involving the left lateral wall of the bladder, extending close to the left ureteral orifice, was disclosed. There was no evidence of extension beyond the confines of the bladder wall. A partial cystectomy was performed with reimplantation of the left ureter into the remaining portion of the bladder.

The postoperative course was uneventful and she was discharged from the hospital 15 days later.

She was last observed August 15, 1948, at which time the cystoscopic examination revealed normal findings. The bladder capacity was 200 cc and the intravenous urograms demonstrated normal ureters and kidneys (fig. 1).

The gross specimen consisted of a roughly circular segment of the bladder wall including the entire thickness removed from the left side of the bladder. The tissue weighed 45 gm. and measured 6 by 5 by 3 cm. On the mucosal side there was a hemispherical tumor mass 4.5 cm. in diameter and 2 cm. in thickness, situated in the mucosa and infiltrating the inner layer of the muscular coat. The tumor was covered by intact mucosa and was composed of soft, white, uniform, cellular tissue throughout.

Microscopic section of the vesical wall showed a diffuse tumor growth of lymphoid type involving the mucous and submucous coats and infiltrating into the muscular coat (fig. 2). The mucosal epithelium was absent except in very small areas. The tumor tissue was of uniform type and similar to that usually seen in lymph nodes. Diagnosis: Lymphosarcoma of bladder (confirmed by Dr. Harry Goldblatt, Dr. Allen Graham and Dr. J. B. Hazard).

ETIOLOGY AND DISCUSSION

The etiology of lymphosarcoma of the bladder, as with other allied neoplasms, remains obscure. Authorities in discussing the histology of the normal bladder differ in opinion as to the presence or absence of lymphoid tissue.

Piersol states that lymphatic nodules are not observed in the normal urinary bladder. In contrast, Bailey states that lymphoid tissue or nodules may be found in the normal bladder.

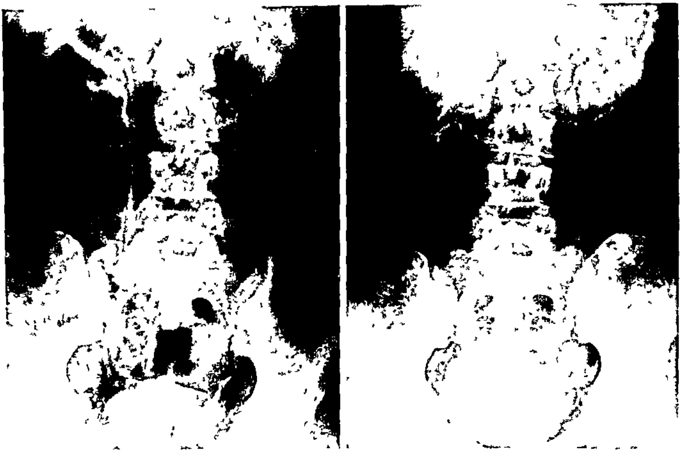

FIG 1 *A*, preoperative intravenous urogram, den
bladder produced by neoplasm Reduplication of r
operative urogram, demonstrating normal upper urin
in bladder

Rathbun and Wehrbein observe: "The extraordinary rarity of lymphosarcoma of the urinary bladder is due to the fact that the normal bladder lacks lymphoid tissue."

An analogous picture was presented in patients with lymphosarcoma of the testes. Ewing states that the testes normally contain no lymphoid tissue. Due, however, to the bilateral involvement, the metastatic origin of lymphosarcoma of the testes must be considered. It is the general conception that lymphoid tissue or nodules may be observed upon microscopic examination of the bladder wall as the result of prolonged infection.

This is substantiated by the observations of Hinman and Cordonnier. In 1935 they presented 10 cases of follicular cystitis. Microscopic examination of the nodules showed them to be composed of lymph follicles. Kretschmer in 1908, in citing a case of cystitis follicularis and glandularis, stressed that lymphoid tissue in the bladder was to be considered part of a coexisting disease of the bladder.

Kreutzmann discusses the role of infection to the presence of lymphoid tissues in the bladder.

Symptoms of cystitis had been present in Eve's patient for several years, while it had existed for 2 years in the patient reported by Chaffey.

The patient of Maragna's had complained of symptoms of cystitis for many years, and the same symptoms had existed for 7 months in the patient of Dupont and Misrachi. In the recent case report of Kreutzmann it was stated that cystitis had been present for several years, while a history of bladder infection for a period of 10 years was elicited from the patient of Rathbun. Although cystitis was present in our patient at the time of examination, no lengthy history of the infection was obtained. Nine years prior to our study the urine examination was normal.

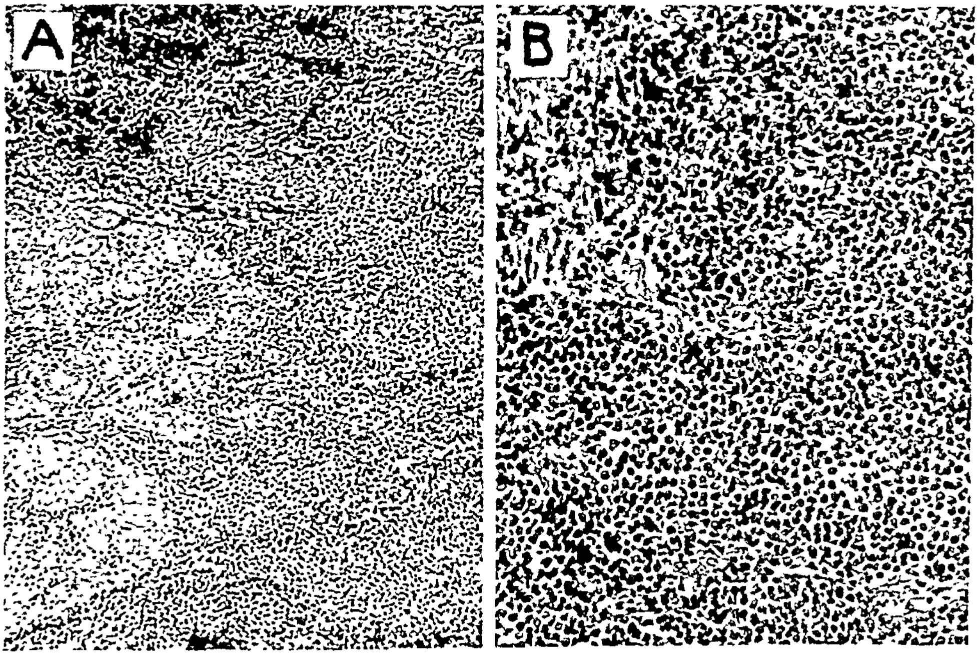

FIG. 2. *A*, lymphosarcoma. Dense, diffuse infiltration of muscularis of bladder wall by tumor (× 70). *B*, lymphosarcoma. Infiltrating mass of small lymphocytes comprising neoplasm (× 200).

Karsner states: "Primary sarcoma of the urinary bladder is rare. Grossly it may be nodular or diffusely infiltrating. Microscopically it may be lymphosarcoma, a spindle cell sarcoma, or one of the differentiated forms of sarcoma. Care must be taken to distinguish a sarcomalike proliferation of connective tissue of papillary tumors or carcinoma derived from papillomas." Rathbun classifies lymphosarcomas into 2 groups: 1) the large cell lymphosarcoma which arises from the germinal center lymphoblasts; 2) the malignant lymphocytoma which consists of a primitive type of lymphocyte.

END RESULTS

The cases presented by Eve and Chaffey were postmortem specimens

The patient observed by Maragna in 1927 died 8 months after operation

Eight months after operation the patient of Dupont and Misrachi showed no evidence of a recurrence

Twenty months after operation, Kreutzmann's patient was living and well Cystoscopic examination revealed no evidence of recurrence This patient received postoperative radiation

The patient reported by Rathbun in 1944 was free of recurrence 6 months later He had received x-ray therapy after operation

Our patient is living and well 11 years after operation and postoperative roentgen therapy The cystoscopic examination shows no evidence of recurrence

CONCLUSION

Lymphosarcoma of the bladder is a rare malignant neoplasm

The seventh case of this type of tumor is reported

Surgical excision followed by postoperative radiation is the treatment of choice for lymphosarcoma of the bladder

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THE STATUS OF IRRIGATING FLUIDS FOR TRANSURETHRAL RESECTION: OUR EXPERIENCE AND A SURVEY OF THE USE OF VARIOUS SOLUTIONS BY OTHERS[1]

G. L. GARSKE, O. C. PHARES AND T. H. SWEETSER

The post-transurethral resection oliguria syndrome has been the subject of much discussion. The entity does not correspond to the usual postoperative oliguria observed with excessive operative blood loss with or without replacement, and the irreversible shock state.

The completely resected good risk patient may develop nausea, anorexia, chills, backache, anemia not commensurate with the operative blood loss, oliguria, progressive azotemia, and occasionally nonobstructive jaundice during or shortly following the procedure. This patient's resection in retrospect probably followed one or two courses, or possibly both: the first characterized by excessive venous hemorrhage from open prostatic sinuses with attempted control by prolonged fulguration at high frequency, increased irrigation pressure, and overdistension of the bladder; or, the second, wherein perforation of the vesical neck or prostatic urethra occurs with extravasation of irrigating media to the periprostatic and perivesical spaces.

The pathologic physiology of the syndrome is certainly not perfectly understood. It is probable that intravesical and intravascular hemolysis of red cells, or the infiltration of periprostatic tissues by a nonisotonic hemolyzing bladder irrigant provokes a specific renal response. McLaughlin postulates the possibility of liberation of a specific nephrotoxic substance from prostatic juices, excessively fulgurated prostatic tissue, or muscle or fat. This substance resembles histamine in its spastic effect on smooth muscle, and could produce renal vasospasm and renal ischemia. Bunge and Barer found over 100 mg. per cent of free hemoglobin in the plasma of 17 of 100 consecutive cases of transurethral resection patients using water as the irrigating medium. Three of the 17 demonstrated severe oliguria and progressive azotemia, with 1 case terminating fatally. Yuile demonstrated a synergistic action of free hemoglobin and renal ischemia with the production of severe renal damage in rabbits. Flink has produced severe renal damage in dogs with very high levels of free hemoglobin. On the other hand, comparable degrees of hemolysis and the intravenous injection of hemoglobin solutions have, in other cases, produced few or no ill effects. No matter what the mechanism may be, it does result in severe anemia with hemoglobinemia and hemoglobinuria terminating in the lower nephron nephrosis observed in blackwater fever, sulfonamide toxicity, severe burns, incompatible transfusion, crush syndrome (myoglobin), etc.

Recent investigation and use of isotonic or hypotonic nonhemolyzing irrigating solutions indicate that such fluids will prevent the oliguria syndrome.

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[1] Read at annual meeting, North Central Section, American Urological Association, Des Moines, Iowa, October 29, 1948.

One recalls that Creevy's report on hemolytic reaction and its treatment and prevention was received with some skepticism at the North Central Section meeting at Rochester 2 years ago. A number of the participants in the discussion indicated they expected to continue the use of water as an irrigant rather than the 4 per cent glucose solution proposed by Creevy. Prophylaxis would take the form of avoiding excessive irrigating pressure, over-distension of the bladder, prolonged fulguration, and deep dissection to or through the prostatic capsule.

Nesbit and Glickman recognized the importance of the oliguria syndrome, although they said it had not been encountered in their clinic in 16 years of transurethral resection. They began the use of a dispensable amino acid, glycine, in a hypotonic 1.1 per cent solution, and have not observed a hemolytic reaction in 1000 cases. They also set forth the essentials of the ideal irrigating fluid:

1) It must be isotonic or nonhemolyzing at hypotonic concentrations. Water is neither. Glucose is nonhemolyzing in solutions greater than 2 per cent. Glycine is isotonic in 2.1 per cent solution, and nonhemolyzing at concentrations greater than 1 per cent.

2) It must be either nonelectrolytic or only weakly ionized. All three irrigants meet this requirement.

3) It must be nontoxic to local tissues and when given intravenously. Water is toxic to local tissues, and hemoglobinemia occurs when it is given intravenously. Glucose is certainly innocuous to tissues and when given intravenously except, of course, in the patient with diabetes mellitus. Glycine is harmless to local tissues and when given intravenously for it is readily metabolized.

4) It must be transparent, or of such translucency that visual acuity is maximum. Water is clear because of hemolysis of red cells. Glucose and glycine become relatively opaque because of suspension of the red cells in a nonhemolytic medium which, paradoxically, is a definite advantage in the control of bleeding.

5) It must be cheap in large quantities. All three meet this requirement.

It took us many months and a perforation, while attempting to control excessive bleeding in an 84 year old patient which terminated fatally in lower nephron nephrosis, before our consideration of a change from water to a nonhemolyzing irrigant became actual instead of academic. The first transurethral prostatectomy with 1.25 per cent glycine was performed in February 1948, and 92 procedures have been completed since that time (tables 1 and 2).

A control series (table 3) using water as the irrigating agent was begun at the Minneapolis General Hospital at the time the glycine series at St. Mary's Hospital was started. Patients of both hospitals received similar pre- and postoperative care, and essentially similar operating conditions existed except for the operative irrigant. Three cases of hemoglobinemia with oliguria syndrome promptly occurred and 1 patient expired from a lower nephron nephrosis as proven by necropsy. The control series was abandoned at 50 cases in August 1948 in favor of 1.25 per cent glycine.

The prompt control of operative hemorrhage is mandatory when using glycine, for uncontrolled hemorrhage renders the medium relatively opaque because of the suspension of red cells without hemolysis. However, this has paid dividends in decreased operative blood loss, because of the more immediate and accurate fulguration necessary to maintain a clear operative field. True, the operating time has been increased a minimal amount in the early stages, but we believe that the advantage of definitely demonstrable hemorrhage at the time when it can be more easily arrested, before an appreciable blood loss occurs, far outweighs the short extension of operating time.

TABLE 1.—*1.25% glycine series from February 22, 1948 to October 1, 1948*

Transurethral resections of prostate	
One stage	78 cases (15 of which were carcinoma)
Second stage	5 cases
	83
Postoperative resections for delayed hemorrhage	
	5 cases
Transurethral resections of bladder tumors	
One stage	3 cases
Second stage	1 case

We began the use of glycine in bladder tumor resection the third week of September, 1948.

TABLE 2

	RANGE	AVERAGE
Operative blood loss	10–1600 cc	267 cc
Weight of resected tissue	1– 52.3 gm.	27 gm.
Operating time	30– 160 min.	84 min.
Amount of 1.25% glycine	10– 42 liters	23.5 liters
Age of patient	47– 92 years	69 years
Height of irrigating fluid above prostate:		
with table not elevated	16– 30 in.	24 in.
with table elevated	10– 24 in.	18 in.

Serum hemoglobin at termination of operation not greater than 5 mg. % in 92 cases.

TABLE 3.—*Water series at Minneapolis General Hospital from February to August 1948*

Average operative blood loss	411 cc
Average weight of the resected tissue	19.5 gm.
Average operating time	94 min.

Serum hemoglobin: 3 of 50 patients had postoperative level greater than 500 mg.%.

The operative and immediately postoperative blood loss with glycine has decreased considerably (table 4), and the effects on the patients have been such that the floor nurses repeatedly voluntarily state that the immediate postoperative condition has been so improved that nursing care is easier and the patient's recovery more rapid. Similar experiences have been reported elsewhere by those using a nonhemolyzing operative irrigant.

Nesbit in his monograph *Transurethral Prostatectomy* discussed the control of hemorrhage from capsular venous sinuses. He noted that such bleeding, although often profuse, occurred only when the venous pressure exceeded the intraurethral pressure of the irrigating fluid. Control of such bleeding by fulguration was usually unsuccessful and time consuming, but control was easily accomplished with the inlying Foley bag catheter. Alcock, in reply to our recent questionnaire received by most of you, supported Nesbit's stand most emphatically. *Hugo Miller, our associate at Minneapolis* General Hospital, goes farther in noting that whenever, for any reason, the venous pressure is lower than the intraurethral pressure of the irrigating fluid, the fluid will be *sucked into* any open vein or venous sinus whether in the prostate or the prostatic capsule. He noted that the Trendelenberg position might easily give a negative venous pressure at the level of the prostate, similar to the negative venous pressure at neck level, which in the past, caused deaths from air embolism during thyroidectomy. If the venous pressure, from any cause, is unusually low and the vein large, a large amount of fluid may enter the venous circulation, unnoticed even when the bladder is nearly emptied. The operator, encouraged by a fairly clear field, may continue resecting under a false sense of security. If the irrigant is water he certainly is begging for intravascular hemolysis.

TABLE 4

	ST. MARY'S	GENERAL HOSPITAL
Average blood loss	276 cc	411 cc
Average operating time	84 min.	94 min.
Serum hemoglobin	less than 5 mg. % in 92 cases	3 of 50 cases greater than 500 mg. %

The cost of glycine (table 5) or glucose is not prohibitive. We procure 50 pound drums at a net cost of 85 cents per pound. Fifty grams of the dry powder is used to make 4 liters of a 1.25 per cent solution for approximately 9 cents. The average case required 23.5 liters at a total cost to the patient of a little more than 50 cents which is cheap insurance for a smooth postoperative course.

The solution may be prepared by 3 methods:

1) Preparation of gallon units of 1.25 per cent solution by the pharmacy to be autoclaved in the operating room.

2) Preparation of a 20 per cent concentrate by the pharmacy to be diluted to the desired concentration in the operating room.

3) We prefer to have the pharmacy weigh 50 gm. units of the dry glycine and box the amount in ½ pint cardboard cartons to be autoclaved in the operating room. These units can then be diluted with sterile water in sterile gallon bottles as needed.

The cost of 4 per cent glucose varies from $1.50 to $4.00 per case. The slightly greater cost, as well as the disadvantages of stickiness of gloves and instruments, and the theoretical danger to the diabetic patient from a transprostatic infusion of glucose, have led us to prefer glycine.

The low cost, availability, and ease of preparation coupled with the lack of evidence of any serious untoward effects of either glycine or glucose should leave little reason for learning the hard way by encountering a bitter experience with a hemolytic reaction.

We have been surprised at the replies to our recent questionnaire, particularly with the several recent publications advocating change to nonhemolyzing irrigating fluids. Of the North Central Section members polled, 88.4 per cent continue to use water as an operative irrigating fluid (table 6).

We are unable to comprehend from these returns why such a situation exists when consideration is made of the work on the oliguria syndrome by Creevy, McLaughlin, Nesbit, Bunge, Dees, etc. We concede that there are arguments in favor of the use of water over a nonhemolyzing solution, but the one factor that water is or can be a lethal agent overrules any favorable point in our opinion. There may be one or several nonhemolyzing solutions better than those now in use. We have other fluids in the laboratory phase of investigation and hope that one of them when in clinical use, may prove to be the ideal irrigating fluid.

TABLE 5.—*Cost of glycine*

Cost per pound (in 50 pound drums)	$0.85
Cost of 50 gm. necessary to make 1 gallon (4 liters) of 1.25% solution	.09
Average case required 23.5 liters	.54

TABLE 6.—*Survey of North Central Section of American Urological Association*

Total letters sent		250
Total letters returned		215
Group I		
Using water only	182	
Using water but changing	1	
Using water—tried glycine but didn't like it	4	
Using water—tried glucose but didn't like it	3	
	190 or 88.4%	
Group II		
Using water and glucose	4	
Using water and glycine	4	
	8 or 3.7%	
Group III		
Using glucose only	11	
Using glycine only	6	
	17 or 7.9%	

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suprapubic tube has been removed and the patient voids through the urethra with some dysuria. He has not had an erection in the past 2 months.

DISCUSSION

Priapism is not the result of any single factor. A multiplicity of factors must enter the picture before a true state of priapism is maintained. Probably the most important single factor is thrombosis. This was first brought out by McKay and Colston who stated that if erection persisted 2 days or more, thrombosis existed in the corpus. However, this is not in the form of a true thrombus, since the material evacuated from the corpus is thick, dark and gummous in consistency, as though the blood were defibrinated. Johannesberg and Donovan offered the theory that prolonged erection and stagnation of the blood could cause defibrination if there were trauma enough to release thrombokinase. They postulated that the fibrin thus freed could obstruct the venous outflow while allowing the filtration of water from the blood and, consequently, lead to an increased viscosity. However, whatever the cause, we do know that the blood is altered with a resultant increased viscosity which helps to maintain the priapism.

Another important factor to consider is a focus of infection. This focus, along with the stagnated blood in the corpus, may well play a part in the formation of a pseudo-thrombosis. Many of the cases presented in the literature gave a history of an upper respiratory infection preceding the onset of the erection or showed evidence of chronic prostatitis or carious teeth in the course of examination. Graves reported a case of what he calls "acute corpora cavernositis," in which there was a definite history of upper respiratory infection accompanied by perineal pain 2 weeks before the onset of priapism. A large percentage of the patients present local and systemic manifestations of infection. There is usually local pain and swelling with temperature elevation.

There must first be a physiological or pathological erection before infection and thrombosis can maintain a state of priapism. The actual physiology of erection will not be discussed here, but suffice it to say that the entire mechanism is initiated by nerve impulses either descending from the higher centers of the brain or ascending from local stimulation. These nerve stimuli may be initiated by lesions of the cord or brain or locally by irritation from inflammation or foreign bodies. The original erection may also be caused by certain blood dyscrasias, such as sickle cell anemia or leukemia, in which there is mechanical blockage of the smaller sinuses in the corpora as well as changes in the central nervous system. Recently, it has been suggested that there may be a motivating factor causing the original erection as a result of the administration of male hormone. Finkler reports a case of priapism lasting 17 days after the administration of 100 mg. of testosterone propionate. Other cases have been reported, but unlike Finkler's case, they all subsided immediately after the withdrawal of the drug. This would lend strength to the theory that in order to have priapism some other factor, such as an infectious process, must be present. In our case the patient received testosterone prior to admission but the last administration was 1 month before the priapism took place, hence, it is doubtful that it played a significant role in this case.

Treatment in priapism is directed, first, towards the relief of the erection, and secondly, towards relief of the motivating condition Immediate relief is best obtained in the manner advocated by McKay and Colston. They suggest aspiration of the corpora cavernosa with a syringe and a large gauge needle. Local heat is applied and one of the sulfonamides and penicillin is given for the infection The sooner the aspiration of the corpora is done, the better will be the ultimate functional result It may be necessary to perform aspiration several times before a lasting favorable result is obtained Incision and drainage of the corpora may be employed, as it was in our case, but the functional result is not as good, since there is considerable secondary scarring To attack the systemic pathology without evacuation of the corpora will not alleviate the condition of true priapism Elimination of the nervous impulse will not do away with the basic underlying pathology, namely, pseudo-thrombosis of the corpora cavernosa

SUMMARY

A case of priapism is presented as an unusual complication of transurethral prostatic resection

An infectious process must be superimposed on an original physiological or pathological erection to maintain a state of priapism

Treatment should be directed, first, towards evacuation of the corpora by aspiration with a large gauge needle and treatment of the infection with antibiotics and heat, secondly, towards elimination of the systemic causes

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BONE MARROW STUDIES IN CARCINOMA OF THE PROSTATE[1]

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It is generally recognized that carcinoma most frequently metastasizes by the lymphatic channels or by the blood stream. Carcinoma of the prostate has been thought to metastasize regionally by the lymphatics and particularly the perineural lymphatics but evidence has been obtained to indicate that dissemination by way of the blood stream is extremely frequent if not the usual route. Hematogenous spread is suggested by the frequency with which metastases may be demonstrated in sternal bone marrow and in other bones remote from the original tumor. Since tumor cells are occasionally found in the bone marrow before anemia or x-ray changes appear, implantation and growth of the tumor seem to occur primarily in the hemopoietic rather than the osseous tissue. The recognition of tumor metastases in the bone marrow by sternal puncture was first reported by Rohr and Hegglin.[2, 3] Since their observation, demonstration of metastatic tumor cells by bone marrow aspiration has been confirmed by many investigators.[4, 5, 6] Hematologic studies have been made by one of us (R. W. R.) in 102 patients with various types of malignancy which had spread locally or produced distant metastasis. In this group, there were 32 cases of carcinoma of the prostate. Bone marrow metastases were found in 18 patients in tissue remote from the prostate gland, 15 of them in the sternum, one in the vertebra and 2 in the ilium. A valuable physical sign was noted in the group of patients in whom tumor cells were demonstrated in the sternal marrow; there was marked tenderness to firm pressure on the sternum.

Bone marrow was aspirated with a No. 16 or No. 18 needle, preferably from areas of increased tenderness over the sternum or elsewhere in areas of x-ray abnormality (fig. 1).[7, 8] Strong suction was applied momentarily and films prepared directly on cover slips from the tip of the needle. Often only a small drop of sanguinous material could be obtained when metastasis had infiltrated the hemopoietic tissues. When no marrow could be aspirated a solid core of tissue was cut out with a needle trephine.[9] This tissue is fixed, sectioned and stained. Satisfactory material was sometimes aspirated after using the trephine. When the sternal marrow was normal and metastases were suspected in more deeply situated bones as in the ilium, vertebral bodies, etc. a long No 18 spinal needle was implanted and its correct position verified by x-ray films before aspiration was carried out. The marrow films were stained best with a buffered Wright's stain.

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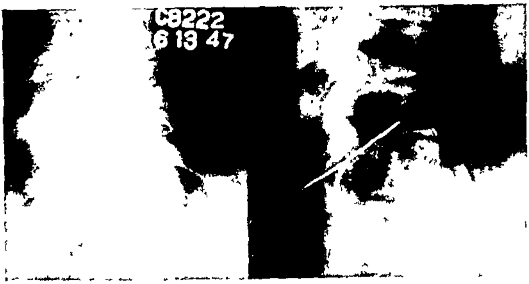

FIG. 1. Picture of needle in vertebra

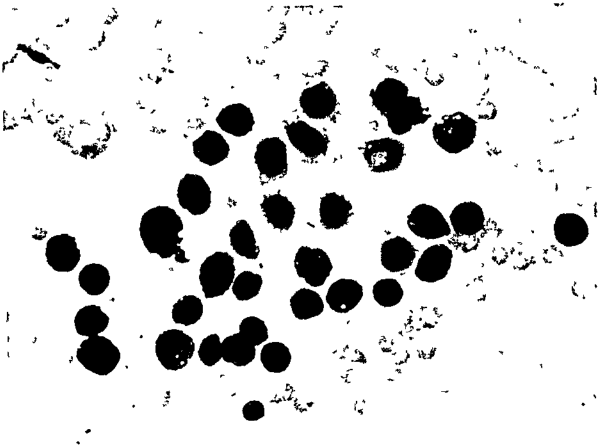

FIG 2 Tumor cell in bone marrow

Tumor cells can be readily identified (fig. 2) in bone marrow preparations by experienced hematologists. The most useful identifying feature is that the tumor cells are foreign cells unlike those normally present or any derived from the marrow in different pathologic states. Tumor cells tend also to adhere to each other in small or large clumps in marrow films in which the other cells are well spread. Not infrequently they occur in circular clumps suggestive of sectioned acini.

Adenocarcinoma cells may be identified as such, but one is unable to differentiate from what particular gland they originate.

Anemia occurs frequently in patients with carcinoma of the prostate. The hemoglobin was less than 12 grams per 100 cc (78 per cent) in 17 of the 32 patients in this group. Tumor metastases were present in 16 of these 17 patients, the other was in uremia and had a very high nonprotein nitrogen. It is recognized among hematologists that senility and general debility of old age is not per se the cause for such low hemoglobin. Bone marrow metastases were demonstrated in 4 individuals who were not anemic. There were 11 patients who had either bone marrow or bone metastasis and whose hemoglobin was not below 12 gm. It is concluded therefore, that an anemia below 12 gm. is suggestive of metastasis. Eight patients with more severe grades of anemia had immature granulocytes or nucleated red cells present in the circulating blood. The latter abnormalities were prominent only when the hemoglobin was reduced to 7.5 gm. or less. Great quantities of tumor tissue were invariably found in the bone marrow of these patients. The anemia is due to the infiltration and crowding of the bone marrow with neoplastic cells.[10, 11]

A BONE MARROW STUDIES AND METASTASIS

METASTASIS		BONE MARROW			
		POSITIVE		NEGATIVE	
		Cases	%	Cases	%
POSITIVE	24	14	58	10	42
QUESTIONABLE	3	3	-	0	-
NEGATIVE	5	1	20	4	80

B

BONE MARROW STUDIES AND ACID PHOSPHATASE

BONE MARROW		ACID PHOSPHATASE			
		Elevated		Normal	
		Cases	%	Cases	%
POSITIVE	18	14	78	4	22
NEGATIVE	14	6	43	8	57

FIG. 3. *A*, bone marrow in cases with metastasis. *B*, bone marrow compared with serum acid phosphatase.

This study was begun with the hope that this procedure might give additional diagnostic assistance in questionable cases. We believe it has proved to be helpful. In a series of 207 cases of carcinoma of the prostate, in which x-rays were made, 57 per cent had evidence of osseous metastases. There were very few cases with extra-osseous metastasis only; 2 to the lungs, 1 to the brain, 1 to the bone marrow

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and 2 to the lymph nodes In a group of 32 patients (fig 3, *A*) who had bone marrow studies, there were 24 with x-ray or biopsy proof of metastasis In 14 of these patients, or 58 per cent, bone marrow metastases were demonstrated It is evident that bone marrow studies are not a short-cut toward proof or disproof of metastases In exceptional cases and in those with questionable diagnosis such studies may be of considerable help There were 5 patients in the group studied hematologically who had no evidence of tumor metastasis and in 4 of these marrow implants were not demonstrated In 1 patient with no evidence clinically, roentgenologically, or chemically of metastasis, implants were discovered in the bone marrow There were 3 others in whom the x-ray evidence of metastasis was questionable The bone marrow was positive in all of these 3 Therefore, in 4 cases in this small series, bone marrow studies were of definite assistance when compared with the x ray examination alone

A comparison of the serum acid phosphatase and bone marrow studies in patients with evident osseous metastasis was made Of 119 patients with roentgen evidence of bone metastasis, 70 per cent had an elevated acid phosphatase In 88 patients with no evidence of bone metastasis, 86 per cent had a normal acid phosphatase and only 3 had a phosphatase above 5 units King Armstrong Evidently it is very rare to have a markedly elevated acid phosphatase without evident x-ray metastasis Of the 18 patients who had demonstrable marrow involvement, 14 or 78 per cent had an elevated acid phosphatase and 4 were normal (fig 3, *B*) The latter is difficult to explain Perhaps the tumor cells were not producing the particular kind of acid phosphatase which is demonstrated by the King Armstrong method On the other hand, 6 or 43 per cent of 14 patients with negative bone marrow had elevated acid phosphatase and 8 had normal phosphatase It must be remembered that only 1 bone marrow aspiration was made on these 6 patients Here again it is evident that the serum acid phosphatase is more reliable as a diagnostic procedure if considered alone However, it is of particular interest to note that 4 patients with a normal serum acid phosphatase had tumor in the bone marrow It is certainly true that the finding of a positive bone marrow in the presence of questionable or negative x ray and/or normal acid phosphatase determination, is of tremendous diagnostic help

From a clinical standpoint then, of what practical value is the bone marrow examination in an individual case? It was of distinct aid in 6 of the 32 patients They are divided into two groups The first three are those in whom the rectal examination was thought to be not carcinoma or very questionable (fig 4, *A*). These patients were examined by several urologists and the majority opinion taken If a judgment had to be given on the rectal examination alone, the gland would be considered as not carcinoma However, when the x-ray and serum acid phosphatase are considered along with the rectal examination, the positive character of one or the other influences both the x-ray or the rectal impressions For instance, if there is questionable carcinoma by rectal examination but x-ray reports definite osteoplastic metastasis to the lumbar spine and sacrum the urologist who formerly reported questionable carcinoma will now agree that it is positive The same is true if this patient has a markedly elevated serum acid phosphatase reported subsequently the clinician will then say that the gland is most likely carcinoma. But in both of these instances, his judgment has been influenced by other positive tests. The x-rays of two of this group showed metastatic carcinoma and one was questionable. The serum acid phosphatase was elevated in 2 and normal in 1. The one patient with questionable x-ray and rectal and a normal acid phosphatase was a hard problem until the bone marrow report was obtained. In all three of these patients, the bone marrow was positive. Therefore, if considered on the rectal examination alone, it was not possible to make a definite diagnosis in any of these 3 patients. Judgment in two of them was influenced by the x-ray and acid phosphatase findings. In 1 case a definite diagnosis could not be made until a positive bone marrow was obtained. The patient McNeill is illustrative of this group. He had a suprapubic prostatectomy a year previous and the pathologic report at that time was benign prostatic hypertrophy. Obstructive symptoms recurred and rectal examination showed a prostate very slightly enlarged and definitely indurated and slightly nodular. It was considered possibly carcinoma but more likely a chronic fibrosis such as one often feels months after a prostatectomy. A definite diagnosis could not be made from the rectal examination alone. The x-ray showed only one localized osteolytic reaction near the hip joint. Roentgenologists could not say definitely that this was metastasis. The acid phosphatase was 2 units King Armstrong. Hence it was

A

BONE MARROW HELPFUL

RECTAL EXAMINATION NOT CA. OR VERY QUESTIONABLE CA.

PATIENT	RECTAL EXAM.	X-RAY METAS.	BLOOD AC. PHOS.	BONE MARROW
Monahan	not ca.	+	15	+
Wilson	not ca.	+	16	+
McNeil	? P.O. supra pubic	+-?	2	+

B

BONE MARROW HELPFUL

RECTAL EXAMINATION_____QUESTIONABLE BUT PROBABLY CA.

PATIENT	RECTAL EXAM.	X-RAY METAS	BLOOD AC. PHOS	BONE MARROW
Freeland	? to +	neg.	1	+
Allen	?	?	1	+
Burney	?	? (glands +)	18	+

FIG. 4. *A*, questionable carcinoma, most likely not; *B*, questionable carcinoma, most likely carcinoma.

necessary in this patient to wait until a bone marrow report was made before a definite diagnosis could be established.

The second group of 3 other patients was those in whom rectal examination was questionable but if one had to make a definite choice it would be "probably carcinoma" (fig. 4, *B*). The x-rays of two of these patients were questionable for metastasis; one was negative. A cervical node from one of them was positive. The acid phosphatase was normal in the first 2 cases and elevated in the third. An illustrative case in this group is Freeland. His rectal examination was very questionable; his x-ray was negative for metastasis and the acid phosphatase was one unit. A definite diagnosis of carcinoma of the prostate could not be made on these three tests alone. Bone marrow studies were reported positive for metastatic carcinoma cells and all question of diagnosis was then removed. In this group, bone marrow study in all three cases was of considerable help in making a definite diagnosis. In the latter two it was of perhaps less help because of the high acid phosphatase and the biopsy of the node. In these 6 patients it is quite evident that the bone marrow studies were of definite diagnostic assistance.

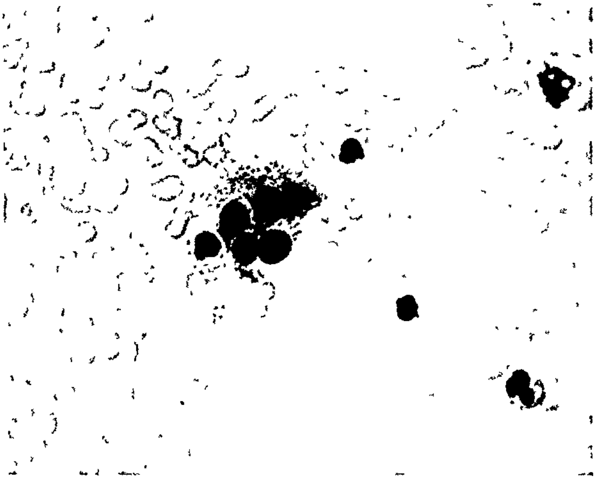

FIG 5. Improvement in bone marrow after hormonal therapy

In addition to this diagnostic aid, the study of the bone marrow may be of considerable prognostic value. Repeated bone marrow studies of patients on hormonal therapy give clear indications, favorable or otherwise, of the course of the disease (fig. 5). A couple of months after castration and the initiation of estrogen therapy the quantity of neoplastic tissue demonstrable by bone marrow aspira-

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TOTAL PROSTATOVESICULECTOMY—RETROPUBIC APPROACH

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The perineal operation for total removal of the prostate is unpopular. Relatively few surgeons have been trained to use this approach and therefore this approach has often been avoided. Attributable to this fact many early carcinomas of the prostate must have progressed to the incurable state. There is only one cure for carinoma of the prostate, and that is early complete prostatectomy. It seems likely that if a more familiar approach could be used which would accomplish Young's concept of a total prostatectomy, the mortality statistics would be influenced favorably. I believe the retropubic approach offers a relatively facile and more definitive method of performing a total prostatovesiculectomy and removing malignant metastases related to the pelvic vessels.

From the observations and experiences gained in the radical treatment of carcinoma of the bladder in which a total prostatectomy, seminal vesiculectomy, cystectomy, and ureteroenterostomy were done in that order it seemed apparent that a total prostatectomy could be performed in much the same manner, by concluding the operation following the vesiculectomy and then performing an anastomosis of the bladder neck and urethra. The feasibility of this procedure was more apparent after the experiences of Millin and Souttar. Souttar reported an instance in which he inadvertently accomplished the removal of the prostate with its capsule while in the process of a retropubic enucleation.

The retropubic approach permits the removal of metastatic glands along the great vessels of the pelvis. Leadbetter et al. have suggested this additional maneuver, in order to complete an operation for carcinoma of the bladder and the prostate. We have to date no generally accepted urological procedure for the radical treatment of carcinoma of the bladder or prostate which approaches the Wertheim operation for carcinoma of the cervix. Present indications are that the retropubic approach may be exploited to this end.

TECHNIQUE

The technique is illustrated in figures 1, 2, 3, 4.

A midline retropubic or a transverse incision is made and carried through the abdominal muscles and trasversalis fascia. The bladder is emptied, per catheter, and the catheter permitted to remain in place. The retropubic pad of fat is bluntly dissected from the anterior surface of prostatic capsule. The puboprostatic ligaments may or may not be seen at this point. With the index finger as a guide, these ligaments may be palpated and then cut, and beginning at the apex, the prostate is digitally freed posteriorly from its surrounding attachments. The urethra is then partially cut and this becomes evident when the catheter becomes visible. An O chromic suture is then placed in the anterior lip of the urethra to be used as a guide and also to later assist in the anastomosis of bladder neck and urethra. The transection of urethra is then accomplished expeditiously and sponges are placed in the prostatic bed and held in situ with a small Deaver retractor to control bleeding from Santorini's plexus and other vessels The seminal vesicles are individually freed and each vas ligated and transected and the bladder neck is then transected Ureteral catheters may be placed in the ureters through the open

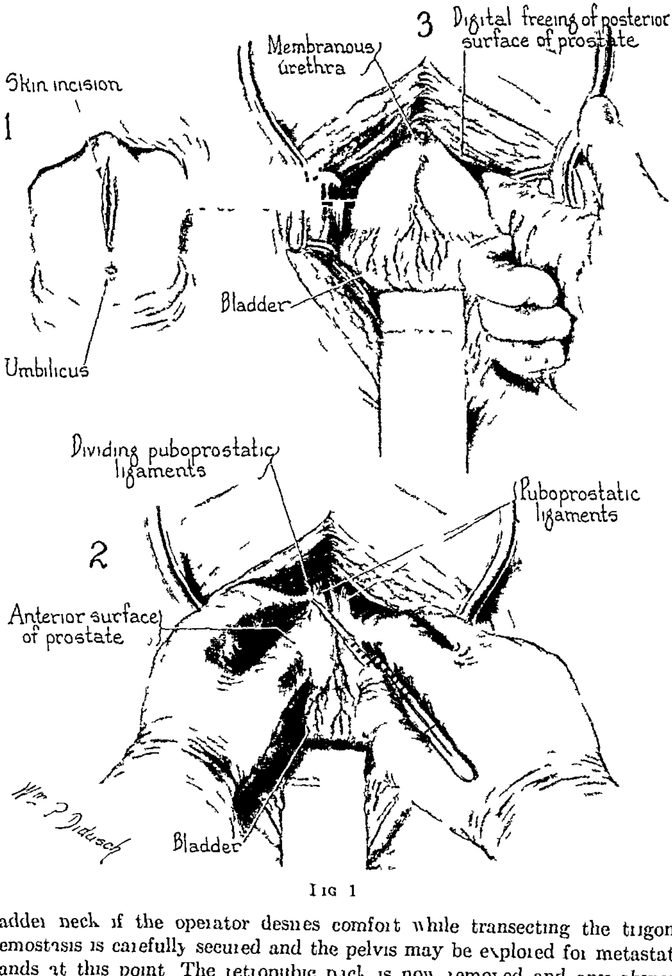
3
Digital freeing of posterior surface of prostate
Membranous urethra
Skin incision
1
Umbilicus
Bladder
Dividing puboprostatic ligaments
Puboprostatic ligaments
2
Anterior surface of prostate
Bladder
Wm P Didusch

Fig 1

bladder neck if the operator desires comfort while transecting the trigone Hemostasis is carefully secured and the pelvis may be explored for metastatic glands at this point The retropubic pack is now removed and any obvious bleeding vessels are secured and ligated or fulgurated The O chromic suture suffering from obstructive prostates, who are in generally good physical condition, who are between the arbitrary ages of 50 to 70 and are sexually indifferent. This would preclude the recurrence of obstruction and decrease the incidence of clinical carcinoma by removing the occult.[1] This seems to the writer to be justified in view of the fact that the morbidity of total perineal prostatectomies as reported by the Johns Hopkins group has compared very favorably with enucleative pro-

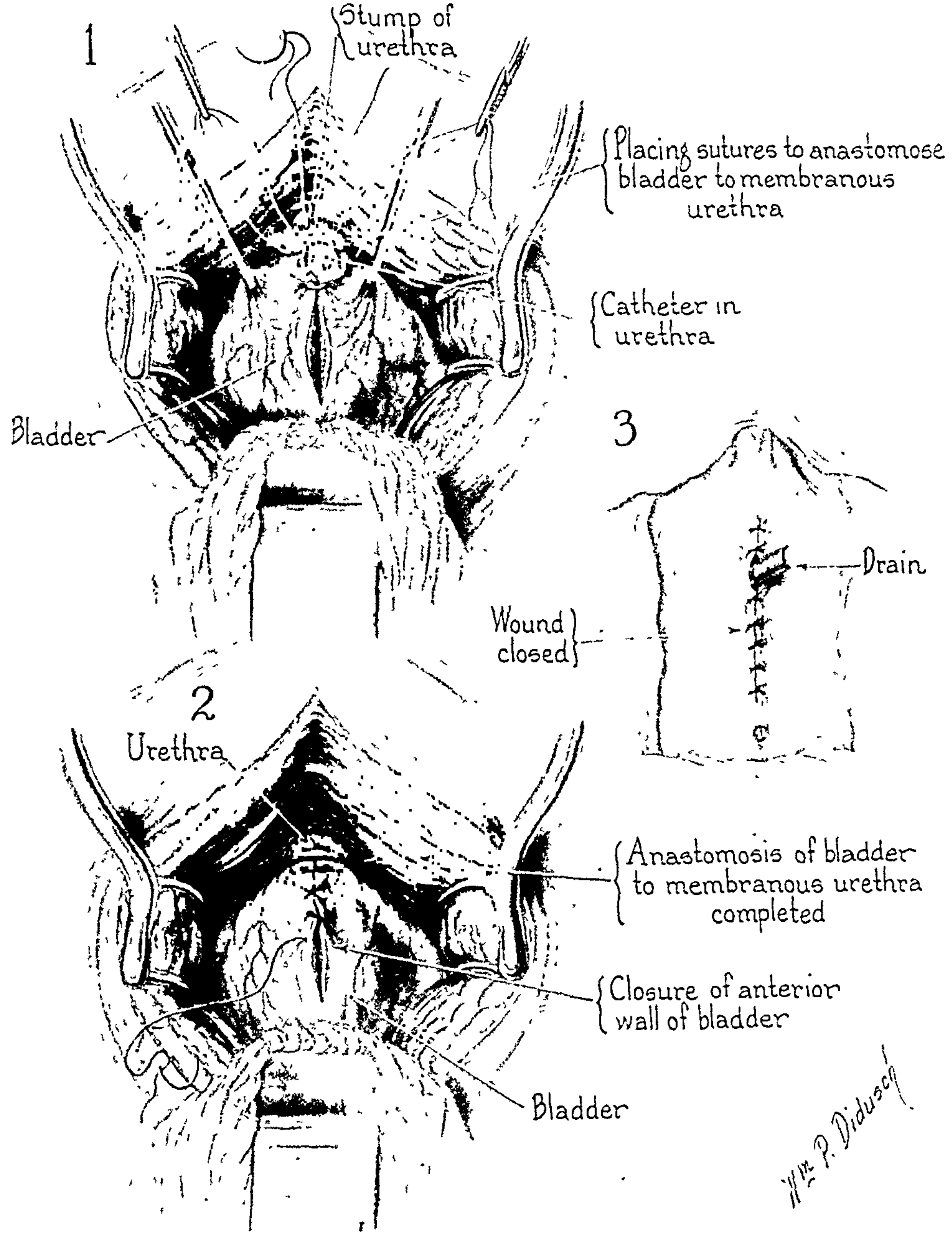
1
Stump of urethra
Placing sutures to anastomose bladder to membranous urethra
Catheter in urethra
Bladder
3
Drain
Wound closed
2
Urethra
Anastomosis of bladder to membranous urethra completed
Closure of anterior wall of bladder
Bladder
Wm. P. Didusch

FIG. 4

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[1] The incidence of occult carcinoma has been given as 46 per cent in 50 consecutive prostates examined completely by Baron and Angrist in men over 50 years of age.

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E HYPOPLASTIC KIDNEY AND THE ATROPHIC PYELONEPHRITIC KIDNEY[1]

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ists always have maintained that conservatism in renal surgery is of t importance. This is best illustrated by 2 cases that were presented oseph Francis McCarthy a few years ago.

n aged 40 years had a large calculus that completely filled the lower the left kidney, causing destruction of this portion of the kidney. A tomy was performed, following which the patient made an uneventful y. About 2 years later, the right kidney was completely destroyed by a obstructive pyonephrosis, necessitating a nephrectomy. Following this d operation, the patient lived 4 years on approximately one half of one y.

boy aged 7 years was admitted to the hospital with a temperature of F and a large mass in the left upper quadrant, together with a history of plete anuria. Dr. McCarthy examined the child. This being prior to the oduction of excretory urography, x-ray study by this means was unattainle. An indigo carmine function test was done, and no dye was seen in the adder. He therefore explored the left flank and noted a large pyonephrotic ss, then did a nephrostomy. There was only a shell of the kidney present. fter the operation, the boy had a rather stormy course, but he lived. Dr. McCarthy's entire staff, including myself, undertook cystoscopy and tried to locate a right ureteral orifice. When excretory urography was introduced, this means was used, and again we were unable to demonstrate a right kidney. The patient lived 12 years and grew to approximately 6 feet in height, weighing close to 190 pounds. His life was maintained on merely a shell of a kidney.

The quantity of kidney substance necessary to sustain life has to date not been established.

There are conditions that demand nephrectomy, although clinically we may be influenced to institute conservative therapy. Among these, we believe should be included the hypoplastic and the infected atrophic kidney. These exert a deleterious effect upon the individual with their toxic by-products and as foci of infection. These kidneys affect hypertension.

The differentiation of the hypoplastic from the atrophic pyelonephritic kidney is not often clinically possible, the one being of congenital origin as a result of development of the renal bud from the wolffian duct, and the other ction and infection of the kidney leading to a contracture and al substance. In both instances the normal kidney has been n life.

oduction of excretory urography, more of these pathological cedures This has also thus far proved to be true in the small number treated by the retropubic route

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[1] eeting, American Urological Association, Boston, Mass., May 18,

The comparison of this procedure with enucleative operations is very favorable Hemorrhage has not occurred postoperatively In all but one instance bleeding from the area of Santorini's plexus has been insignificant If the operation proceeds expeditiously up to and including the transection of the urethra, the operative bleeding is not more than that observed in enucleation procedures All patients receive blood prophylactically when the operation starts The incidence of infection is less, probably because the reservoirs of infection are removed, namely the prostate and seminal vesicles Morbidity as observed in the few patients thus far treated has been minimal Patients have been ambulatory beginning the second or third day Catheters have been removed on the tenth day Following this there has been some stress incontinence in one half of the patients which lasted from 1 to 2 weeks There has been no suprapubic drainage after the tenth day Wounds have healed readily The operating time varied directly with the familiarity of the procedure from 2½ hours initially to 1½ hours for the last three In one instance 1 hour sufficed In the first 3 patients the seminal vesicles were not removed The operator wished to become more familiar with the prostatectomy before proceeding to do the vesiculectomy However, the writer believes careful attention should be given to the vesiculectomy and legation of the vasa In one instance, 3 weeks following his operation, a patient returned for his check-up examination and at this time he was found to have small bilateral scrotal abscesses at the distal end of the vasa Following incision of the abscesses he had a small persistent drainage which resembled urine The drainage eventually ceased after 10 days and has not recurred since No cases of osteitis pubis have occurred to date

CASE REPORTS

Mr H , aged 70, had a diagnosis made of *obstructive carcinoma of the prostate* by digital examination, after he gave a history of prostatism and a residual urine of 4 ounces Operation Total prostatectomy using retropubic approach, refused orchiectomy Placed on stilbestrol mg 6 per diem Foley catheter remained in place 10 days Wound healed 10 days postoperatively Discharged with good urinary control, 17 days postoperatively No sutures were used in approximating bladder neck and urethra The Foley bag was used to effect the approximation Pathological report Carcinoma of prostate, grade 3 Five months check up revealed patient with minimal complaints He had gained weight Appetite was good Urethra dilated to 26 F, without difficulty Ten month check up revealed sustained good urinary control without stress incontinence Moderate bladder neck contracture

Mr H , aged 76, had a diagnosis made of obstructive carcinoma of the prostate by digital examination together with a history of prostatism and a residual urine of 6 ounces Operation Total retropubic prostatectomy Foley catheter was removed on the tenth day Wound closed on the eighth day Patient had been ambulatory since the third postoperative day Patient suddenly expired on the twelfth postoperative day, presumably from pulmonary infarct or coronary thrombosis. No autopsy could be obtained. Pathological report: Marked fibrosis and hyperplasia of prostate; no evidence of malignancy.

Mr. C. S. was aged 71. The pathological diagnosis of carcinoma of prostate was made after the patient had been subjected to a transurethral prostatectomy for a clinically benign obstructive prostate. Operation: Total prostatectomy. Wound healed on the ninth day. Discharged with stress incontinence on fourteenth postoperative day. Three weeks check-up revealed good control, nocturia 9. Had small, bilateral scrotal abscesses at distal ends of vasa. Urine clear. Three month check-up revealed no complaints. Urethra dilated to 26 F sound without difficulty. Gained weight. Good appetite. This patient had stress incontinence for 2 weeks following discharge from hospital. At end of 6 months patient had sustained continence. Pathological report: Carcinoma of the prostate, grade 2–3.

Mr. R. was aged 69. The diagnosis of obstructive carcinoma of the prostate was made by digital examination, with history of prostatism and residual urine of 15 ounces. Prostate suggested malignant nodule. Total retropubic prostatovesiculectomy was done; refused orchiectomy. Postoperative course was excellent; no bleeding. Pathological report: Adenocarcinoma, grade 2. One month check-up revealed good sphincter control; nocturia 9. Patient is taking stilbestrol. There was sustained good sphincter control 8 months postoperatively.

Mr. B., aged 25, had a diagnosis made of irritative prostate. He had been subjected to a transurethral prostatectomy 1 year previously, but his irritative symptoms persisted. A total retropubic prostatovesiculectomy was performed. In 10 days the Foley catheter was removed and the patient was discharged 2 days later with good sphincter control, feeling very happy with the results of the operation. Pathological report: Benign hyperplasia of prostate. Five months postoperatively the patient had sustained good urinary control.

Mr. R. was aged 60. Diagnosis: ? Carcinoma of prostate by digital examination. Operation: Total retropubic prostatovesiculectomy. Foley catheter was removed in 10 days. Wound healed on the fourteenth postoperative day. The patient had moderate stress incontinence which was aggravated by chronic cough and bronchial asthma. He was discharged on his eighteenth postoperative day with an incontinence bag. Pathological report: Adenocarcinoma of prostate, grade 2. Seven month check-up revealed satisfactory urinary control. Patient "leaks a few drops on certain days", and only if he strains or coughs excessively.

Mr. C. was aged 58. Diagnosis: Chronic prostatovesiculitis; obstructive benign prostate, producing a persistent low grade pyuria. Pyeloureterograms normal. Operation: Total prostatovesiculectomy. Pathological report: Chronic infection of prostate and vesicles with many depositions of lymphocytes and polymorhonuclears; some hyperplasia of prostate. Monthly check-ups for 5 months revealed good urinary control.

Mr. J. B. was aged 73. Diagnosis: Carcinoma of prostate, by digital examination. Operation: Total prostatovesiculectomy; refused orchiectomy. During the operation brisk hemorrhage occurred while operator was in the process of freeing prostate from its surrounding fascia preparatory to transecting the urethra. Foley catheter was removed in 10 days. There was moderate stress incontinence.

An anterior urethral stricture had to be dilated following operation In 3 weeks patient had good urinary control and had no complaints Suprapubic wound was completely healed 12 days postoperatively Patient was discharged on his twenty-first postoperative day Pathological report Carcinoma of prostate, grade 3 Two month check-up revealed clear urine and good urinary control At eighth month check up patient had sustained good urinary control

Mr M was aged 58 Diagnosis ? Cancer of prostate The patient had had a bladder papillary carcinoma fulgurated 1 year previously Operation Total prostatectomy, cystectomy, bilateral ureteroenterostomy On opening the bladder to place ureteral catheters, there were recurrences of papillomata found near the bladder neck on the anterior bladder wall, which appeared to be papillary carcinoma, and which were not evident on cystoscopy At this time a change in plan seemed advisable, the operation was extended, and cystectomy and bilateral uretero enterostomy were performed Pathological report Carcinoma of prostate and transitional cell carcinoma of bladder The patient was discharged on the twenty eighth postoperative day

Mr O T was aged 76 Diagnosis Carcinoma of prostate, clinically Operation Total prostatovesiculectomy Catheter removed in 12 days Wound healed in 12 days He was discharged on his fourteenth postoperative day in good condition, with good urinary control Pathological report Benign hyperplasia of prostate with many areas of chronic inflammation and fibrosis A 6 month check-up revealed good urinary control

Mr J A was aged 67 Diagnosis Carcinoma of prostate by digital examination Operation Total prostatovesiculectomy Patient was sexually indifferent Suprapubic wound healed in 10 days Mild stress incontinence for 5 days after removal of Foley catheter He was discharged on sixteenth postoperative day Pathological report Benign hyperplasia of prostate with areas of fibrosis and chronic inflammation Four month check up revealed good urinary control

SUMMARY

In summary, there is evidence to support the contention that total prostatectomies may be done successfully using the retropubic approach It is a desirable approach because it is more familiar to the average urological surgeon than the perineal route It permits a relatively facile and more definitive method of treating carcinoma of the prostate The morbidity compares favorably with other prostatic surgery Although stress incontinence occurs in certain patients it has disappeared in all after a relatively short period The suggestion is made that total prostatectomies be done in patients who are sexually indifferent and who are in the younger prostatic age group even though at the time the gland is apparently benign There is some indication that a certain proportion of patients develop a moderate degree of bladder neck contracture, but thus far have responded without difficulty to the usual dilations Whether this group will contain a greater number of contractures than enucleative procedures must be determined later In the first case where definite bladder neck contracture occurred, no sutures had been used to approximate the urethra and bladder neck.

ADDENDUM

Since my initial experience with this approach in November of 1947, approximately 30 similar cases have been subjected to this operation. To date all patients are living. There has been 1 case of postoperative hemorrhage that was controlled satisfactorily without a secondary procedure. I believe one patient suffered from a mild osteitis pubis 4 months postoperatively. There were 4 instances of bladder neck contracture in which spasm seemed to play a role. The cases in which spasm predominated had been castrated and the question is posed whether this may not be a "withdrawal" symptom.

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LEIOMYOSARCOMA OF THE EPIDIDYMIS: CASE REPORT

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Malignant tumors arising from the testicle proper or its adnexa are rare, comprising only about 0.6 per cent of all malignant tumors in the male population (Herman). In the foreign literature, the incidence is about 1 in every 1,000 to 2,000 male admissions (Herman, Smith). At the Peiping Union Medical College Hospital, Lu and Chai reviewed approximately 200,000 male patients between the years 1921 and 1940 and found 48 cases of primary testicular tumors, an incidence of approximately 1 in every 4,000 patients.

The most generally accepted classification of testicular tumors is that of Hinman. The following table is modified from Hinman's classification:

- I. Homologous neoplasms
  - A. Benign
    - 1. Epithelial: Adenoma of seminal vesicle, epididymis and tunica vaginalis.
    - 2. Mesoblastic: Fibroma of cord, tunica vaginalis and epididymis. Leiomyoma of the cord, tunica vaginalis and epididymis. Hemangioma and lymphangioma of epididymis, tunica vaginalis and tunica albuginea.
  - B. Malignant
    - 1. Epithelial: Seminoma of seminiferous tubules. Adenocarcinoma of epididymis.
    - 2. Mesoblastic: Fibrosarcoma of testis, epididymis and tunica vaginalis. Leiomyosarcoma of epididymis and tunica vaginalis.
    - 3. Lymphoid: Lymphosarcoma (Mathé).
- II. Heterologous neoplasms
  - A. Benign: Dermoid cyst.
  - B. Malignant: Teratoma.

More than 90 per cent of testicular tumors are malignant, among the most common ones are the seminoma and teratoma. Sarcoma is extremely rare. Thompson found only 10 cases of sarcoma of the epididymis and 17 cases of sarcoma of the tunica vaginalis in his extensive review of the subject. All the 27 cases were histogenetically fibrosarcomas. Recently, we encountered a case of leiomyosarcoma arising most probably from the epididymis. The rarity of the condition warrants this report.

CASE REPORT

A Chinese man aged 50 was admitted to the Tientsin Third Municipal Hospital on August 11, 1947 because of a growing mass in the left side of the scrotum of 2 years' duration. About 2 years ago, he had tumbled down from a rickshaw. Immediately after the accident, he noted dragging pain and a mass in the left side of the scrotum. Soon afterwards it grew slowly at first, but then more rapidly reaching the size of a fist in the last 3 months. Libido was much diminished. There was moderate loss of weight and strength.

The patient was normally developed and fairly well nourished. Lungs were clear and negative for metastasis by roentgenological examination. The abdomen contained no palpable mass. Locally, there was a firm mass in the left side of the scrotum, measuring about 13 by 9 by 6 cm. Its surface was nodular, slightly tender and hard in consistency. It was freely movable from the surrounding structures and the overlying skin. The superficial scrotal veins were engorged. Several enlarged lymph nodes were palpable in the left inguinal region. The right testicle and groin were normal. The hemoglobin was 83 per cent, red blood cells 3,900,000, white blood cells 8,000, blood Kahn test negative and normal urine and stool. Friedman's test of urine was not done.

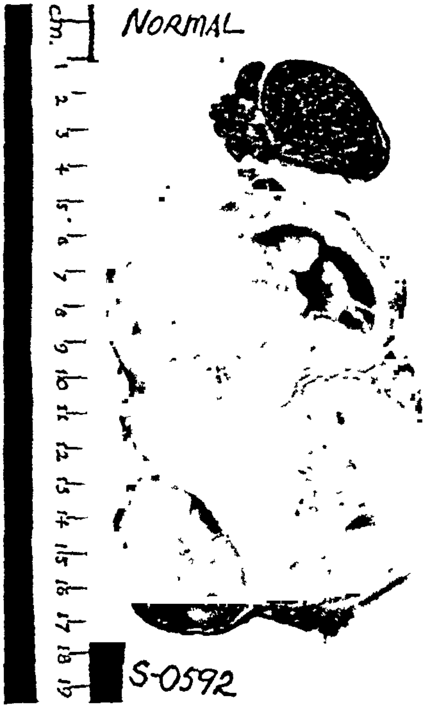

FIG. 1. *Photograph, showing size and location of tumor, and its relation to testicle. Region of epididymis is occupied by two cystic cavities.* (× ⅓)

Excision of the tumor and dissection of the inguinal and iliac lymphnodes were done on August 16, 1947 under spinal anesthesia. The postoperative course was uneventful and the patient was discharged 9 days after the operation.

The specimen consisted of a large, firm, nodular and well encapsulated tumor mass, measuring 12.5 by 8.5 by 6.5 cm. in size (fig. 1). On its lower pole, it was covered by a piece of scrotal skin, measuring 9.5 by 5 cm. The cut surface of the mass showed many interlacing lobules of tumor tissue, separated by pale greenish fibrous stroma. Areas of hemorrhage were seen in the upper portion of the tumor. The testis proper was displaced to one side by the tumor.

It measured 3 8 by 1 by 1 5 cm and grossly appeared to be normal Along the side of the testis there were irregular cystic areas, distended with greenish mucoid material. The largest one measured 3 5 by 1.8 by 2 2 cm They probably represented some of the dilated epididymal tubules, as rudiments of atrophic epididymis could be seen in the upper portion.

Microscopically, the testicular tissue appeared normal The cystic areas were proved to be the dilated tubules of epididymis lined by cuboidal or flattened epithelium The tumor tissue consisted of large sheets of spindle shaped cells arranged irregularly in bundles or whorls, interlacing with each other (fig 2) Giant cells were seen occasionally The nuclei were hyperchromic, mostly oval and elongated in shape, with many mitotic figures A few dilated thin walled blood vessels were seen in the stroma between tumor cells By Masson's trichrome stain, the tumor cells were stained purplish with dark nucleated reddish fibrils within the cells, the fibrous stroma was blue and scanty Diagnosis leiomyosarcoma arising from epididymis.

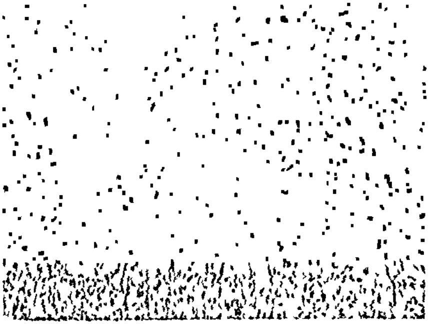

FIG 2 Photomicrograph, showing tumor composed of spindle cells in bundles (×110)

DISCUSSION

Smooth muscle fibers are normally present in the epididymis It also occurs in the wall of the blood vessels of the testis proper. However, smooth muscle tumor arising from blood vessels wall is distinctly unknown Occasionally, one may also find smooth muscle fibers in the tunica vaginalis But the likelihood of the tumor arising from such an origin in this case is rather remote. In all probability, the tumor in this case was derived from the epididymis

As a whole, tumors of smooth muscle origin are relatively rare Malignant leiomyosarcoma is even rarer Of the 6981 cases of uterine myoma reviewed by Novak, the incidence of malignant degeneration was only 0 56 per cent. Benign and malignant leiomyomas may also occur infrequently in the gastrointestinal tract In the epididymis, tumors of smooth muscle origin are exceedingly rare Smith, in discussing tumors of the epididymis, mentioned only 6 cases of benign leiomyoma Thompson stated that tumors of the epididymis were so rare that their existence was of more academic than clinical significance. The latter author collected only 8 cases of benign leiomyoma of the epididymis from the literature. In his series of 13 epididymal tumors, none belonged to that category. Searching in the more recent available literature, we failed to find any malignant smooth muscle tumor of the epididymis. We, therefore, believe that the case reported here is a unique one of a leiomyosarcoma of the epididymis.

Leiomyosarcoma in general occurs in elderly persons. This fact was observed in the uterus and the gastro-intestinal tract (Rabinovitch, Grayzel, Suyer and Pines; Cattell and Colcock). Our patient is 50 years of age. The age distinction is important because of the fact that other more common, particular tumors, such as the seminoma and teratoma, occur most frequently in the younger patients (Herman; Smith, Lu and Char).

Cryptorchidism was frequently considered to be an important factor in the genesis of malignant tumor of the testicle (Lu and Char; Rea; Murray and Ewert), particularly seminoma or embryonal cell carcinoma. In this case, there was no such history. The local trauma before onset was probably a coincidence rather than the cause of the development of the growth.

The symptoms and signs of leiomyosarcoma of the epididymis are those of the testicular tumors in general. Besides the tumor mass, there may be variable degree of pain. Libido may be diminished, but the mechanism of this change is not clear. Unlike seminoma or embryonal carcinoma, the Friedman's test is of little value in the diagnosis of tumors of mesoblastic origin.

The treatment of tumors of the testicle has been unsatisfactory. Although long years of cures have been reported, yet in general the 5 year survival rate varied between 6 per cent and 17 per cent, even in the hands of specialists (Dean). Radical dissection of the lymph-nodes is of questionable value because of the usual bilateral metastatic involvement and early blood stream metastases. Barringer, based upon a study of autopsy material, reported that 72 per cent involved the intra-abdominal organs. At present, the best treatment that can be offered consists of simple resection and wide preoperative and postoperative radiation with deep roentgenrays, regardless of the presence or absence of clinical metastasis (Pendergrass, Chamberlin, Selman and Horn). Early recognition remains to be the most important factor for any chance of cure.

SUMMARY

A case of leiomyosarcoma of the epididymis is reported. It is an extremely rare condition and the case report might be considered the first one of its kind in the literature.

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IDIOPATHIC (SCHÖNLEIN) PURPURA ASSOCIATED WITH HEMATURIA

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Hematuria constitutes one of the most significant symptoms in urologic practice. While in the vast majority of instances the underlying cause is an intrinsic lesion of the urogenital tract and easily ascertainable through routine urologic diagnostic procedures, it may on rare occasions be due to a systemic derangement, especially one involving the hemopoietic mechanism. To ascertain the cause here may tax the diagnostic ingenuity and acumen of the urologist to the utmost. Although mention is frequently made in medical literature of idiopathic purpura as a cause of hematuria, a careful study of the pertinent literature reveals little, if any, direct reference to the condition as related to hematuria. It is a logical assumption, therefore, that most affected patients are treated by internists and are rarely referred to the urologist for the purpose of ascertaining the specific status of the urogenital tract. While hematuria may be a prominent symptom in idiopathic purpura and the success in controlling bleeding is directly dependent upon the efficacy of treatment to eradicate the underlying cause of the purpura, it is possible that the hematuria may, in certain instances, be entirely unrelated to the purely medical condition. It is obvious then that unless the urologic lesion is discovered and removed, the hematuria will not be influenced in any way by the treatment administered for the basic condition. In view of the fact that a patient with Henoch's or Schönlein's purpura, owing to the presence of hematuria sufficient to mask other symptoms referable to the disease, may first consult a urologist, it is important that he be able to recognize the essential features of idiopathic purpura in order to avoid unjustified and often disastrous surgical procedures. The purpose of this paper is to restate the pertinent characteristics of idiopathic purpura with special reference to hematuria, and to report an interesting case of Schönlein's purpura associated with persistent hematuria.

Idiopathic purpura, as the name denotes, is a recurrent clinical entity occurring in patients with no known blood abnormality, and characterized by purpura frequently associated with visceral exudative lesions which give rise to disturbances of joint function and symptoms referable to various viscera.

Henoch described cases presenting intestinal crises (Henoch's purpura); while Schönlein noted patients who presented purpuric lesions associated with joint manifestations (Schönlein's purpura).

ETIOLOGY

The occult condition may occur at any age, in both sexes and in all races, but is most frequently seen in children and young adults. Some conditions are undoubtedly caused by infection. Several have been described as presenting manifestations of allergy.

PATHOLOGY

The underlying pathologic change is an increased permeability of the small blood vessels, permitting extravasation of unusual quantities of plasma and blood elements into the tissues The consequent specific lesions (purpura, edema, erythema) are always focal and depend entirely upon the character of the blood elements that escape No known reason has ever been advanced to explain adequately the distribution of the focal lesions

Although much time has been devoted to the study of the blood and blood-forming organs in the disease, no constant changes have been noted Bleeding and coagulation time, clot retraction and platelets are usually within normal limits Varying degrees of anemia may be present, depending upon the severity of the purpura or loss of blood from the kidneys or gastro intestinal tract

SYMPTOMS

Symptoms are entirely dependent upon the anatomic distribution of lesions In examples of purpura simplex the only manifestation is an extravasation of blood into the skin, conjunctivae or mucous membranes If this is associated with changes in the joints, the clinical entity is called Schonlein's purpura or purpura rheumatica When the extravasation involves viscera such as the bowel, patients complain of severe abdominal pain (Henoch's purpura) Various combinations of skin, viscera and joint manifestations may occur, or a patient may at one time complain of joint pains alone, and at another time of purpuric skin stigmas, erythema, or visceral symptoms Skin eruptions, diffuse or localized, may appear, persist for several days, disappear, and then recur at intervals varying from weeks to years Some patients may reveal the characteristic clinical picture of acute rheumatic fever, the disease is ushered in with sore throat, fever, general malaise and late polyarthritis The skin manifestations may then appear long after all the previously mentioned symptoms have disappeared, persist for a few days, only to reappear at intervals of a few weeks with or without arthritic manifestations

It is reasonably certain that in some patients with skin eruptions or joint pains there occurs a concomitant extravasation of plasma or cellular elements into one or more viscera, with or without symptoms referable to involved organs Visceral changes, almost always confined to the kidneys or bowel, may antedate the general clinical picture of idiopathic purpura by weeks, months or years Foci, or extravasation into the intestine or kidneys, are usually preceded by a moderate elevation of temperature and a feeling of general malaise Symptoms of involvement of the intestinal tract are usually diffuse colicky abdominal pain often associated with diarrhea and melena of variable severity

Renal involvement usually gives rise to hematuria, albuminuria and occasionally a mild degree of renal impairment, frequently leading to an erroneous diagnosis of acute nephritis Hematuria may last a few days to a few weeks, and may lead to varying grades of anemia, at times sufficiently severe to require blood replacement The hematuria may overshadow the clinical picture so as to completely obscure other symptoms Following an attack the urine becomes

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IDIOPATHIC (SCHÖNLEIN) PURPURA ASSOCIATED WITH HEMATURIA

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Hematuria constitutes one of the most significant symptoms in urologic practice. While in the vast majority of instances the underlying cause is an intrinsic lesion of the urogenital tract and easily ascertainable through routine urologic diagnostic procedures, it may on rare occasions be due to a systemic derangement, especially one involving the hemopoietic mechanism. To ascertain the cause here may tax the diagnostic ingenuity and acumen of the urologist to the utmost. Although mention is frequently made in medical literature of idiopathic purpura as a cause of hematuria, a careful study of the pertinent literature reveals little, if any, direct reference to the condition as related to hematuria. It is a logical assumption, therefore, that most affected patients are treated by internists and are rarely referred to the urologist for the purpose of ascertaining the specific status of the urogenital tract. While hematuria may be a prominent symptom in idiopathic purpura and the success in controlling bleeding is directly dependent upon the efficacy of treatment to eradicate the underlying cause of the purpura, it is possible that the hematuria may, in certain instances, be entirely unrelated to the purely medical condition. It is obvious then that unless the urologic lesion is discovered and removed, the hematuria will not be influenced in any way by the treatment administered for the basic condition. In view of the fact that a patient with Henoch's or Schönlein's purpura, owing to the presence of hematuria sufficient to mask other symptoms referable to the disease, may first consult a urologist, it is important that he be able to recognize the essential features of idiopathic purpura in order to avoid unjustified and often disastrous surgical procedures. The purpose of this paper is to restate the pertinent characteristics of idiopathic purpura with special reference to hematuria, and to report an interesting case of Schönlein's purpura associated with persistent hematuria.

Idiopathic purpura, as the name denotes, is a recurrent clinical entity occurring in patients with no known blood abnormality, and characterized by purpura frequently associated with visceral exudative lesions which give rise to disturbances of joint function and symptoms referable to various viscera.

Henoch described cases presenting intestinal crises (Henoch's purpura); while Schönlein noted patients who presented purpuric lesions associated with joint manifestations (Schönlein's purpura).

ETIOLOGY

The occult condition may occur at any age, in both sexes and in all races, but is most frequently seen in children and young adults. Some conditions are undoubtedly caused by infection. Several have been described as presenting manifestations of allergy.

companied by low backache, pain in the right loin and thigh, and subconjunctival hemorrhages Each attack persisted approximately 14 days, and then subsided for intervals of 6 to 12 months During intervals he was completely asymptomatic The present attack began a few days ago with pains in legs and joints, and subconjunctival hemorrhage followed by hematuria

Cystoscopy disclosed a few petechial hemorrhages around the right ureteral orifice, and red blood cells in urine specimens from both kidneys The bladder urine was grossly bloody The remainder of the urologic examination was essentially negative

Urinalysis Specific gravity 1 020, *p*H 6 0, albumin 1 plus, sugar negative, bile negative, microscopic, loaded with red blood cells

Blood chemistry Creatinin 1 8 mg /per cent, urea nitrogen 11 6 mg /per cent, uric acid 2 25 mg /per cent, urea clearance 81 7 per cent, calcium 6 6 mg / per cent, phosphorus 2 1 mg /per cent

Fishberg concentration test First specimen—specific gravity 1 020, albumin 3 plus, no casts, second specimen—specific gravity 1 022, albumin 3 plus, no casts, third specimen—specific gravity 1 022, albumin 3 plus, no casts

Blood count (May 8, 1947) Hemoglobin 81 per cent, red blood cells 4,070,000, white blood cells 12,400, color index 1 01, segmented polys 55 per cent, lymphocytes 45 per cent

Sedimentation rate 6 mm in 1 hour Blood Wassermann negative

Bleeding time 3 minutes, 45 seconds Clotting time 10 minutes, 10 seconds Prothrombin time Control 18 seconds, test 21 seconds, 81 per cent of normal Clot retraction time complete in 4 hours

Blood culture sterile

Bacteriology Specimens from bladder and both kidneys were negative on smear and sterile on culture

A 2 hour phenolsulphonphthalein test totaled 86 per cent

Physical examination disclosed an extensive left subconjunctival hemorrhage mesial to the cornea Blood pressure 130/80 Rectal temperature 99 6 F, weight 142½ pounds No other abnormal signs

May 12, 1947 For the past 4 days patient had had severe painless hematuria Bone marrow biopsy (Dr N Rosenthal)

Blood count	Hemoglobin	77 per cent
	RBC	4,910,000
	WBC	8,500
	Platelets	170,000
	Polys (nonsegmented)	9 per cent
	Polys (segmented)	45 per cent
	Polys (eosinophiles)	4 per cent
	Lymphocytes	36 per cent
	Monocytes	6 per cent
Bone marrow	Nucleated cells	168,000
	Megakaryocytes	110
	Myeloblasts	2 per cent
	Myelocytes neut	26 per cent

Myelocytes eos.	4 per cent
Polys (nonsegmented)	22 per cent
Polys (segmented)	11 per cent
Polys (eosinophiles)	2 per cent
Hematogones	2 per cent
Lymphocytes	12 per cent
Erythroblasts	5 per cent
Normoblasts	14 per cent

"There is a slight increase in megakaryocytes. These show a tendency to immaturity. Many megakaryoblasts are present, but the pro-megakaryocytes and megakaryocytes already show evidence of platelet formation."

May 21: Hematuria persists.

Blood count:	Hemoglobin:	89 per cent
	RBC:	5,070,000
	WBC:	8,800
	Platelets:	150,000
	Polys (nonsegmented)	4 per cent
	Polys (segmented)	65 per cent
	Polys (eosinophiles)	1 per cent
	Lymphocytes	26 per cent
	Monocytes	4 per cent

Bleeding time 2 minutes.
Coagulation time 8 minutes.
Tourniquet test negative.
Clot retraction present.

May 22: 10 cc of autogenous blood injected intramuscularly.

May 24: 10 cc of autogenous blood injected intramuscularly, plus 0.4 cc of moccasin snake venom.

May 27: Hematuria persists. 5 cc of 1 per cent Congo-red intravenously.

May 31: Patient asserts that hematuria ceased following injection of Congo red. 5 cc Congo-red intravenously.

June 6: Urine negative. Subconjunctival hemorrhage slightly less.

Blood count:	Hemoglobin:	79 per cent
	RBC:	3,870,000
	WBC:	12,600
	Platelets:	130,000
	Polys	65 per cent
	Lymphocytes	31 per cent
	Eosinophiles	3 per cent
	Monocytes	1 per cent

Bleeding time 4 minutes.
Coagulation time 4 minutes.

July 2: Complains of pain in groins, over base of sacrum and in both knees. Examination of knees shows no swelling, redness or limitation of motion. Ecchymotic spots on outer aspect of right inguinal region and outer aspect of upper part of left thigh. Area of ecchymosis on left upper lid. Conjunctival hemorrhages lessened. Temperature taken at four-hour intervals by patient showed slight elevation—100.2 F. Urinalysis negative. Spleen not felt.

July 9: Complains of pain over lower sacrum radiating to groins and down to both knees. Pain in hamstring muscles of both thighs, but none in calves. Temperature 100.6 F. Extensive subconjunctival hemorrhages both eyes. Urinalysis negative.

Blood count:	Hemoglobin:	71 per cent
	RBC:	3,540,000
	WBC:	9,000
	Polys	76 per cent
	Lymphocytes	24 per cent

Sedimentation rate: 5 mm. in 1 hour.

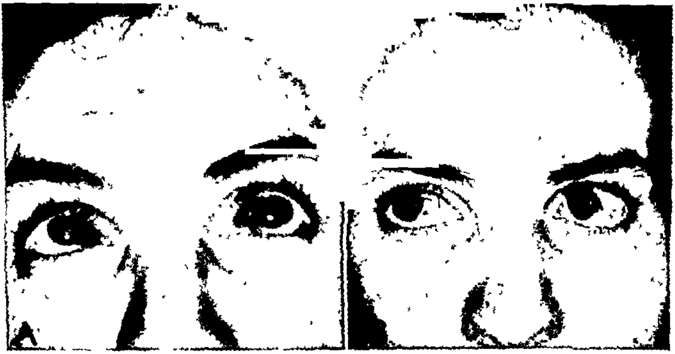

FIG. 1 *A*, showing bilateral subconjunctival hemorrhages before treatment. *B*, showing bilateral subconjunctival hemorrhages following treatment.

Roentgenologic examination of both knees and lumbosacral spine: No pathologic changes in knees. Spina bifida occulta fifth lumbar vertebra and first sacral segment.

July 16: Severe pain in back, thighs and knees. Small doses of deep roentgen therapy to back and knees.

July 23: Pain in back and knees greatly relieved, but now complains of severe pains in both temperomandibular joints, making it difficult to chew. Has developed flareup of subconjunctival hemorrhages. Deep roentgen therapy administered to both temperomandibular joints and to both knees and sacrum.

July 26: Severe attack of hematuria commenced this morning; 5 cc of 1 per cent Congo-red intravenously. Deep roentgen therapy to both temperomandibular joints.

July 30: Hematuria persists. Pain in temperomandibular joints no longer present, and patient is able to chew without discomfort. No pain in back or knees, but complains of ache in left ankle and left quadriceps muscle. Ecchymosis of left lower lid. Extensive subconjunctival hemorrhages (left); 5 cc of 1 per cent Congo-red intravenously, 0.4 cc moccasin snake venom subcutaneously. Deep roentgen treatment to anterior aspect of left thigh and left ankle.

Diagnosis: In view of the absence of a primary lesion in the urogenital tract, or of any alterations in the hematopoietic system or blood clotting mechanism, and because of arthralgia affecting several joints, our diagnosis was Schönlein's purpura with hematuria as one of the outstanding manifestations. The patient was referred to Dr. N. Kugelmass to ascertain food sensitization. The examination showed sensitivity to rice, wheat, veal, chocolate, nuts, raw vegetables and fruit. Removal of these foods resulted in a prompt and complete abatement of all symptoms.

August 12: Completely asymptomatic. Urinalysis negative.

Blood count:	Hemoglobin:	90 per cent
	RBC:	4,530,000
	WBC:	6,700
	Polys	60 per cent
	Lymphocytes	39 per cent
	Eosinophiles	1 per cent

SUMMARY AND CONCLUSIONS

Idiopathic purpura is a recurrent clinical entity, usually occurring in children and young adults, and characterized by purpura associated with joint or visceral symptoms due to exudation of plasma and blood elements into the tissues, and unaccompanied by any clinical changes in the blood. Where the predominant changes occur in the skin or conjunctivae, the condition is called purpura simplex. Henoch's purpura is the term applied to the clinical complex where visceral symptoms predominate. Purpura associated with joint or muscle symptoms is called Schönlein's purpura. Hematuria may occur as a secondary or dominant symptom in any of the previously mentioned syndromes. It may precede, follow, or occur in association with the other symptoms characterizing the general variety of purpura. There is no specific therapy. In view of the fact that several manifestations of allergy are presented by many patients, elimination of specific foods is clearly indicated. A 1 per cent solution of Congo-red intravenously has also been found effective in arresting hematuria temporarily.

Idiopathic purpura is one of the rare causes of hematuria. The paucity of case reports of the condition appearing in the literature of urology is probably due to the fact that the majority of the patients come within the province of the internist because of prevalence of symptoms other than hematuria, and are therefore never referred to the urologist. However, in some patients hematuria constitutes the chief symptom of the disorder and completely obscures the clinical picture. The urologist may then be the first to see the patient. He must, therefore, be cognizant of the outstanding features of the condition in order to avoid errors in diagnosis and unnecessary and at times hazardous surgical procedures.

An interesting case of Schönlein's purpura with severe hematuria is presented, where symptoms promptly disappeared following elimination of offending foods.

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THE MEDICAL MANAGEMENT OF PREMATURE EJACULATION

LAY AYCOCK

Premature ejaculation during sexual intercourse is a masculine complaint which brings many patients to physicians Its cause and treatment have long been puzzling Urologists have sought for local causes, usually finding none except congestion of the verumontanum, if even this Treatment by local applications to this area is of as little avail as most other medical measures heretofore proposed, including hormone administration The family physician, the urologist, and the patient himself, alike discouraged at the lack of improvement, often finally turn to the psychiatrist

Whether or not Freudian by bent, the psychiatrist tends to regard premature ejaculation as a potentially serious neurosis Thus, for example, Diethelm[1] who says, in discussing "Psychic Impotency"

"In the beginning premature discharge (ejaculatio praecox) due to anxiety and less frequently to psychic hyperesthesia, may occur only occasionally, then increase in frequency, and finally lead to total impotency In many cases we find a more or less marked personality maladjustment or a well defined psychoneurosis " There follows a 12 page discussion of psychiatric treatment

Recent evidence suggests that "psychoneurosis", if present, is usually a result of premature ejaculation, rather than its cause The patient, believing that the phenomenon is abnormal, worries over its occurrence and persistence, and is further fixed in the belief that something is seriously wrong with him by the physician's efforts to get at the root of his trouble, and by the elaborate psychiatric ritual of treatment Approaching the problem from the taxonomic standpoint, however, Kinsey[2] reports that premature ejaculation is not "abnormal", at least in the sense that it is not unusual Says he, in discussing "Speed of Male Orgasm"

"For perhaps three quarters of all males orgasm is reached within 2 minutes after the initiation of the sexual relation, and for a not inconsiderable number of males the climax may be reached within less than a minute or even within 10 or 20 seconds after coital entrance This quick performance of the typical male may be most unsatisfactory to a wife who is inhibited or natively low in response, as many wives are, and such disparities in the speed of male and female response are frequent sources of marital conflict, especially among upper social levels where the female is most restrained in her behavior Nevertheless, the idea that the male who responds quickly in a sexual relation is neurotic or otherwise pathologically involved is, in most cases, not justified scientifically "

Whether usual masculine behavior or not, it is however true that the phenomenon of premature ejaculation is a source of dissatisfaction to many men and to their wives, and that a continuation of it may result in a vicious circle of social, sexual, and mental difficulty

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[1] Diethelm, O Treatment in Psychiatry New York The Macmillan Co , 1936, p 408

[2] Kinsey, A C , Pomeroy, W B and Martin, C E Sexual Behavior in the Human Male Philadelphia W B Saunders Co , 1948, p 579 ff

The purpose of this paper is to suggest a simple form of medical treatment which has been satisfactory in many cases, and which deserves a trial in all before more prolonged, expensive (and often unsatisfactory) methods of psychiatric treatment are undertaken.

Dibucaine hydrochloride (Nupercaine hydrochloride-Ciba)[3] is a local anesthetic acting like cocaine when applied to mucous surfaces. It is marketed as an ointment (nupercaine 1 per cent in an anhydrous lanolin base). When this ointment is applied copiously to the glans penis, prepuce, and adjacent shaft* (paying especial attention to the corona and frenum), there ensues, in about 20 minutes, partial but not complete anesthesia which lasts about 3 hours. The anesthesia does not abolish tactile sensation, but only dulls it; and it does not interfere with turgescence and erection.

If sexual intercourse is undertaken at the height of anesthesia or toward its end, i.e., 2 to 3 hours after application of the ointment, intromission may usually be effected without premature ejaculation. The average male, if able to delay orgasm for as long as the first minute or two, is thereafter able to exercise at least partial subsequent control, and to prolong the act for whatever period of time, usually 10 to 30 minutes, necessary for his partner to reach the climax simultaneously with him. The mild anesthetic effect of the nupercaine neither prevents orgasm in the male, nor diminishes its intensity.

The ointment does not irritate the delicate mucosa of the glans and prepuce. Repeated applications over a period of years have not resulted in any examples of allergic sensitization to nupercaine. There is no anesthetic effect on the vaginal mucosa of the sexual partner, since before intercourse, the penis may be washed free of all remaining ointment and dried.

It will be objected that the procedure introduces a psychologic hazard in that it demands advance planning as to sex relations, and application of the treatment 2 to 3 hours before the act. This objection is no greater, however, than applies to the feminine preliminaries of diaphragm and contraceptive jelly; and is in most cases surmountable.

SUMMARY

The local application to the penis of 1 per cent nupercaine ointment is suggested as a successful method of treatment of many cases of premature ejaculation.

Medical Arts Bldg., Baltimore 1, Md.

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[3] New and Non-Official Remedies, 1948. Philadelphia: J. B. Lippincott Company, pp. 49–50.

* The clothing may of course be protected by wrapping the anointed penis in toilet paper for an hour or so, until absorption is complete.

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INFLAMMATORY REACTIONS INVOLVING SPERM AND THE SEMINIFEROUS TUBULES EXTRAVASATION, SPERMATIC GRANULOMAS AND GRANULOMATOUS ORCHITIS

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There has been considerable interest in recent years in the physiology of sperm, particularly with regard to infertility However, published morphologic studies have dealt almost entirely with abnormalities of the spermatozoa of men who were infertile or had hypogonadism Little work has been done on the peculiar reactions of tissue to extravasated sperm, such as those catalogued in the article by Oberndorfer in the Henke-Lubarsch Handbuch[1] and those noted, in 1941, by Orsos[2] and, more recently, by Steinberg and Straus [3]

Curiosity about the consequences of spermatic extravasation was aroused at the Army Institute of Pathology in 1944, on receipt of a specimen removed from a man who had cystic swelling at the site of a vasectomy some years after the operation was performed Microscopic examination revealed a granulomatous fibrohistiocytic reaction with phagocytosis of sperm Subsequently a number of similar granulomas were observed (fig 1), some were isolated lesions, while others were complications of other processes, such as tuberculosis of the epididymis Twelve specimens in which the pathologic pattern was dominated by the formation of granulomas subsequent to the extravasation of sperm have been collected It is the purpose of the present report to describe these reactions and to discuss the biologic significance of the phenomena observed

The clinical and pathologic data in the individual cases follow

CASE REPORTS

Case 1 (No 104670) A 66 year old man underwent prostatectomy and bilateral vasectomy for adenocarcinoma of the prostate Orchiectomy was performed 3 years later Pathologic data The testes were atrophic, both testis and epididymis contained healed infarcts Macrophages loaded with basophilic material formed a granuloma in the epididymis A few giant cells were present, some adjacent to basophilic concretions Other basophilic masses were composed of aggregated sperm, masses of sperm lay interstitially and in a lymphatic Histiocytes containing brown pigment and fat, and eosinophiles infiltrated a cicatrix which marked the site of a group of destroyed tubules

Case 2 (No 106230) One year after a 34 year old man was injured on an obstacle course a lump developed in the spermatic cord A diagnosis of fibroma was made and the mass removed Pathologic data The fragment of tissue,

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[1] Oberndorfer, S Die inneren mannlichen Geschlechtsorgane In Henke, F , and Lubarsch D , Handb d spez path Anat u Histol , Berlin, Julius Springer, Vol 6, pt 3 , 1931

[2] Orsos F Die Spermainvasion Virchows arch f path Anat , 307, 352-361, 1941

[3] Steinberg, J and Straus, R Sperm invasion of the epididymis J Urol , **57** 498-503, 1947

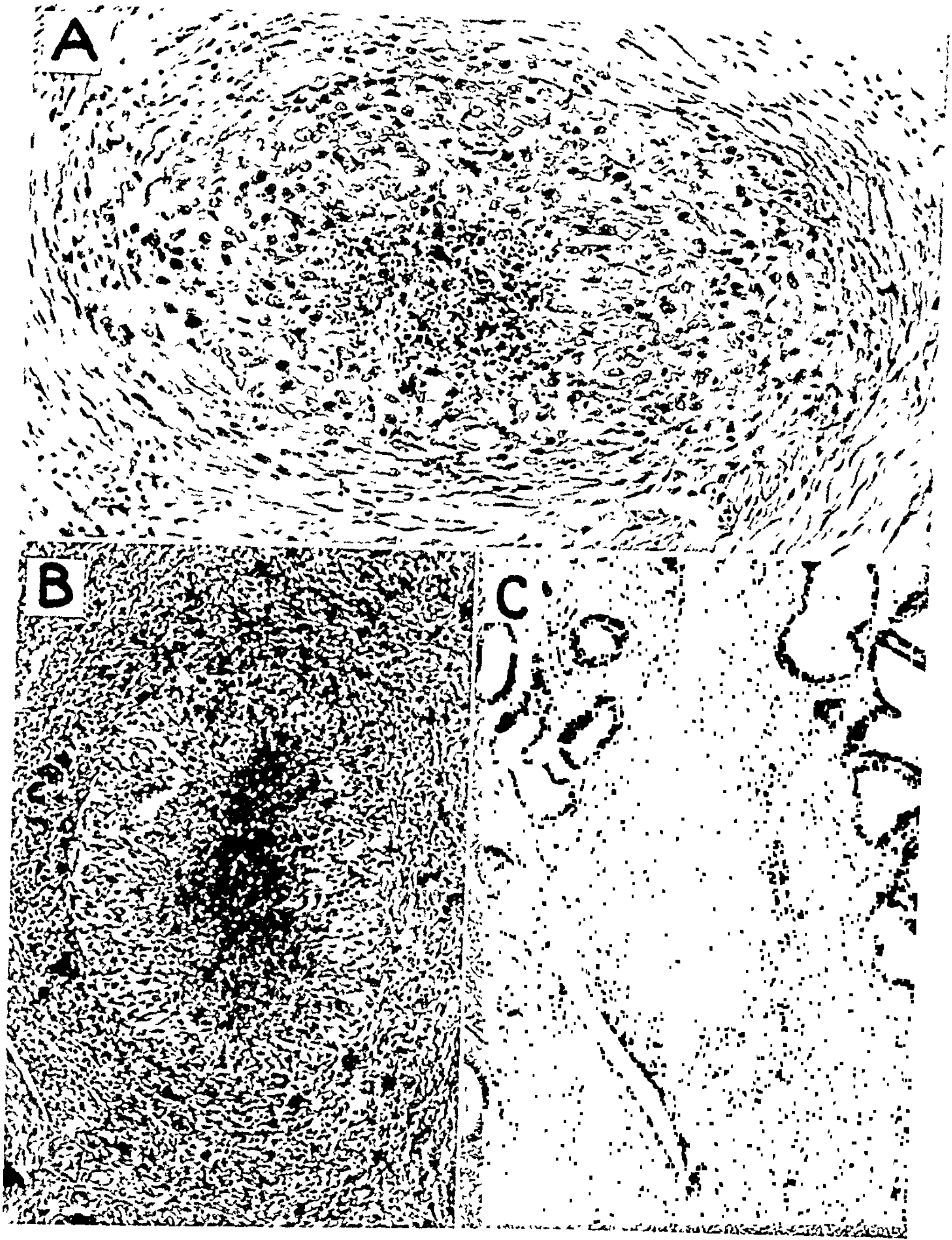

Fig. 1. *A*, (negative 102355, AIP 106230) Spermatic granuloma. A collection of macrophages surrounds a mass of sperm. × 185.

B, (negative 98233, AIP 177513) Tuberculoid spermatic granuloma. A central mass of débris and sperm is surrounded by a zone of macrophages. Basophilic concretions and giant cells are present in outer fibrous wall. × 115.

C, (negative 100427, AIP 158830) Spermatic granuloma. Central necrotic débris and sperm of this lesion resemble caseous center of a tuberculous nodule. ×30.

0.7 cm. in greatest diameter, was composed largely of whorled nodules of lamellated collagen surrounding central pools of free sperm. Ducts were distorted by tuberculoid granulomas, masses of histiocytes loaded with sperm and basophilic granules. Some nodules undergoing fibrosis contained no sperm.

Case 3. (No. 126968.) Several years after vasectomy a 23 year old man had painful swelling at the operative site. For 1 month the mass slowly increased in size. Pathologic data: Microscopically, the cystic structure, which was 0.5 cm. in greatest diameter, resembled the specimen in case 2. There were free sperm in the interstitial tissues, histiocytes were more abundant and fibroblasts were fewer. Sperm and brown pigment granules were present in the epithelial lining of the wall of the cyst.

Case 4. (No. 154083.) A man had a hydrocele for 4 years; routine study disclosed acid-fast organisms in his urine. The hydrocele sac and portions of the epididymis were removed. Pathologic data: A cavity in the epididymis, measuring 0.5 cm. in greatest diameter, contained gray fluid resembling pus. The dilated tubules of the epididymis were filled with sperm, other cellular elements and eosinophilic droplets. Multinucleated spermatic elements were present in the tubules. A pool of sperm in the tissues surrounding the ducts was walled off by macrophages, some of which contained sperm.

Case 5. (No. 158830.) A "tumor" of the epididymis was removed from a 31 year old man. There was no history of previous urologic operative procedures. Pathologic data: Grossly, only a tiny yellow nodule in the epididymis was visible. Microscopically, leukocytes and foreign body giant cells were evident about suture material in one section. The dilated tubules of the epididymis contained mononuclear cells, spermatocytes and multinucleated spermatic elements. Similar cells, some of which appeared to be degenerating, and eosinophilic droplets were present in an extratubular pool of sperm. In the surrounding wall of macrophages were many phagocytosed sperm. A single well defined tuberculoid granuloma contained a central mass of eosinophilic débris, miscellaneous cellular elements and sperm. Basophilic granules filled many cells in its fibrohistiocytic wall.

Case 6. (No. 177513.) The right testis and epididymis of a 31 year old man were removed, because of tuberculosis, and a resection of the left vas was carried out. The left epididymis was removed 2 years later. Pathologic data: Several nodular swellings were evident on the surface of the epididymis, and small white tubercle-like foci were disclosed on section. Microscopically, discrete and confluent tuberculoid granulomas were observed. Pools of sperm were surrounded by palisaded macrophages loaded with sperm. Masses of granular and amorphous basophilic material lay outside the phagocytic wall. Occasional giant cells were encountered, some of which contained basophilic material.

Case 7. (No. 185329.) The right testis of a 29 year old man who had had an enlarging painful mass in the right epididymis for 10 days was removed after the diagnosis of tumor was made clinically. Pathologic data: Examination disclosed a firm nodular swelling of the head of the epididymis and proliferation of granulation tissue on the surface of the tunica. Microscopic study revealed densely cellular tissue simulating a neoplasm, but the aggregations of round and spindle cells contained many phagocytes loaded with sperm.

Case 8. (No. 187280.) A 34 year old man was hospitalized for 2 years because of a fractured femur. He injured his testicle during the application of a leg brace, and the testis became painful and swelled to 3 times its normal size.

Because of a clinical diagnosis of tumor the testis was removed. Pathologic data: The epididymis was hard and "fibrotic" and contained poorly defined small yellow nodules. Microscopically, the few dilated tubules contained sperm, spermatic aggregates and phagocytes. There was marked dilatation of the rete testis. Focal intertubular collections of lymphocytes were noted, some of which contained sperm. Viable testicular tubules were found embedded in coagulated exudate in the vaginal space.

Case 9. (No. 188735.) A 35 year old man had a tender swollen testicle for 6 weeks. The epididymis was resected. Pathologic data: A nodule, 0.5 cm. in greatest diameter, at the superior pole of the epididymis, resembled a tubercle. There were slight dilatation of the tubules and periductile fibrosis. In the interstitial tissues was a large pool containing sperm, mononuclear cells, leukocytes and eosinophilic droplets. Another small collection of sperm was observed in one of several foci of interstitial cellular infiltration.

Case 10. (No. 191220.) A 30 year old man died from a gunshot wound in the head. Pathologic data: There was malformation of the vasa deferentia and of the seminal vesicles, which exhibited hypoplasia. The extremely dilated tubules of the epididymis were filled with fluid, sperm, spermatic aggregates and phagocytes. Accumulations of macrophages formed granulomas in and about the tubules; some bulged into the lumens beneath intact epithelium, and others were in direct contact with degenerating masses of sperm. Cholesterol slits, masses of free brown pigment and brown granules in macrophages and epithelial cells were encountered.

Case 11. (No. 193070.) A 33 year old man underwent low inguinal vasectomy. A sinus formed at the operative site and drained intermittently; occasionally it closed and a painful mass developed. One year later an "inflammatory mass" of the vas was resected; it contained turbid fluid, thought to be purulent. Pathologic data: In a section of vas 2.5 cm. long was a rounded mass, 1.5 cm. in diameter, which on cross section showed brown pigmentation of the center and scarring of the periphery. Microscopically, there were fibrohistiocytic accumulations with an occasional suggestion of a central cavity. Well defined granulomas were formed by phagocytes containing sperm surrounding masses of free sperm.

Case 12. (No. 193844.) A 23 year old man had a hard lump at the inferior pole of the right testis, inseparable from the epididymis. Although the clinical diagnosis was fibroma, at operation a diagnosis of dermoid cyst was made. Pathologic data: The epididymis showed interstitial cellular infiltration. There were one large and several small extratubular collections of sperm surrounded by the typical wall of macrophages.

PATHOGENESIS

Extravasation was attributable to a definite factor in 7 of the 12 cases. Four granulomas followed resection of the vas deferens, and 2 developed after injury to the testis; spermatocele resulting from "compensatory" dilatation of the epididymis was responsible in a single instance. In the other 5 cases the etiologic background was more obscure, although antecedent epididymitis (case 9), trauma (case 8) and undisclosed operation (case 5) can reasonably be incriminated.

In the uncomplicated ty [illegible] 2 cases reported here, sperm reach [illegible] (fig. 2, A) and provoke a reaction (fig. 2, B). In rare instances, as in cases 7 and 8, the sperm penetrate even into the serous space begween the tunics. In the mixed types the granuloma results after a process such as tuberculosis has destroyed the walls of the tubules and permitted their contents to come in contact with surrounding tissues.

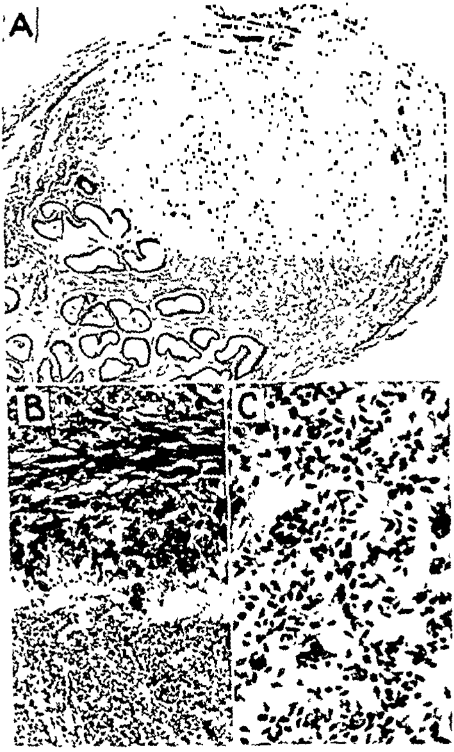

FIG. 2. *A*, (negative 99759, AIP 158830) Extravasation of a large amount of sperm has produced a cystic mass in epididymis. × 20.

B, (negative 98414, AIP 181838) A wall of sperm-laden phagocytes surrounds a pool of extravasated sperm × 185.

C, (negative 101337, AIP 181838) *There is diffuse extravasation of sperm into interstitial tissues.* × *600.*

In the interstitial tissues (fig. 2, *C*) many sperm are taken up by macrophages. Both phagocytosed and free sperm may persist for long periods. Occasionally the sharply outlined heads of the sperm in the histiocytes are replaced by basophilic granular masses which are presumably degradation products of the spermatic nucleoproteins (fig. 3, *A*). The heads of the sperm give a positive Feulgen reaction but do not react with Schiff's reagent after treatment with periodic acid. The granular material, on the other hand, gives a negative reaction to the Feulgen test, but after exposure to periodic acid and Schiff's reagent it turns brilliant red. The occasional large deeply basophilic concretions within or adjacent to giant cells in old granulomas (fig. 3, *B*) react positively to von Kossa's stain and negatively to the Prussian blue stain. In the present series concretions were present in some cases in which extravasation had occurred 2 or 3 years before the lesions were examined.

Unaltered sperm were present for at least a year after injury in case 2. Sperm may have persisted in the interstitial spaces for several years in case 3, but the occurrence of another extravasation cannot be excluded.

DIAGNOSIS

Spermatic granulomas may simulate tumors of the testis or epididymis or, when there are much pain and swelling, epididymitis. For example, in the present series a preoperative diagnosis of fibroma of the cord was made twice, and in a third case the lesion disclosed by operation was diagnosed as dermoid cyst. At operation, the diagnosis of an inflammatory process is often made because spermatic granulomas resemble tubercles and their cloudy fluid content may appear to be a purulent exudate.

However, the correct diagnosis should easily be established, both clinically and pathologically, and it may even be made grossly. The diagnosis of spermatic granuloma should be entertained whenever there are pain and swelling of the epididymis or vas after trauma or surgical manipulation. Identification of sperm in smears of the "exudate" may have practical diagnostic value.

COMMENT

Detailed knowledge of the fate of unexpelled sperm in man would shed much light on the processes initiated by extravasation, but few established facts are available in spite of a great amount of speculation and investigation. Simeone and Young[4] expressed the idea, on the basis of experimentation with guinea pigs, that sperm are not voided and are not resorbed, either in the epididymis or in the seminal vesicle. They stated that the aging of sperm and their exposure to increasingly higher temperatures during passage along the vas were responsible for the degeneration and liquefaction which they noted in the vas and epididymis. Wilhelm and Seligman[5] presented evidence that in men the seminal tract normally empties to some degree by flow into the posterior portion of the urethra, independent of ejaculation. Oberndorfer[1] expressed the opinion that the

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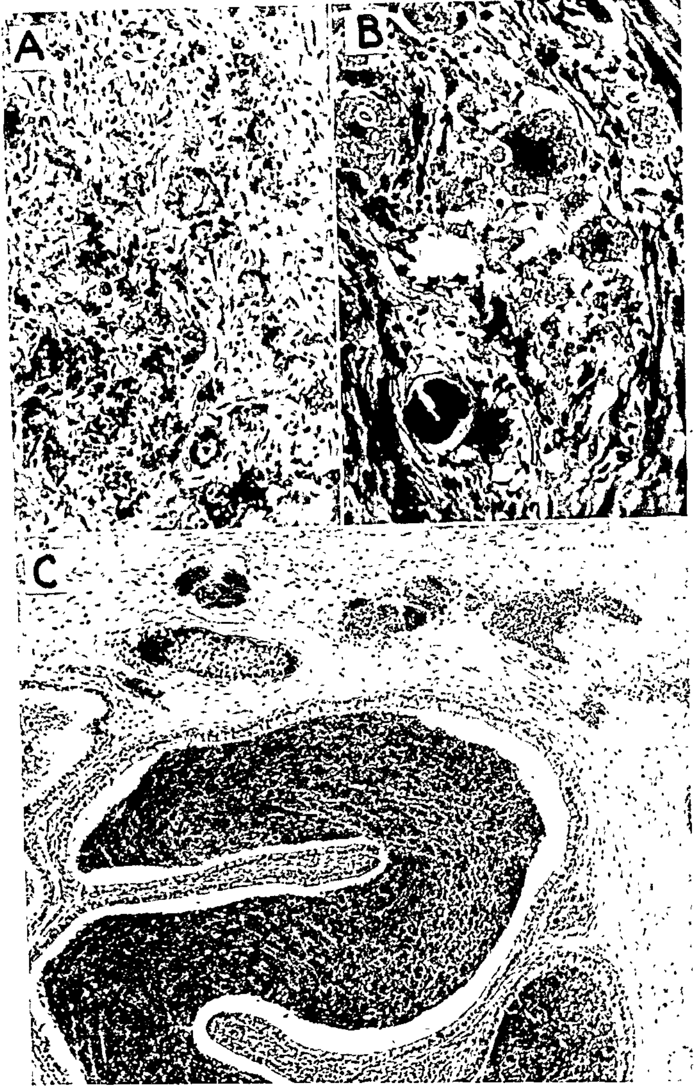

FIG. 3. *A*, (negative 100066, AIP 177513) Outer wall of a spermatic granuloma contains *giant cells and intracellular and extracellular basophilic granular material which is possibly* altered spermatic nucleoproteins. × 235.

B, (negative 99768, AIP 104670) Macrophages and giant cells containing finely granular basophilic material and basophilic concretions are evident in an old spermatic granuloma. × 250.

C, (negative 99754, AIP 147150) Spermatocele of epididymis. Masses of sperm fill nearby lymphatics as well as dilated ducts. × 55.

In the interstitial tissues (fig. 2, *C*) many sperm are taken up by macrophages. Both phagocytosed and free sperm may persist for long periods. Occasionally the sharply outlined heads of the sperm in the histiocytes are replaced by basophilic granular masses which are presumably degradation products of the spermatic nucleoproteins (fig. 3, *A*). The heads of the sperm give a positive Feulgen reaction but do not react with Schiff's reagent after treatment with periodic acid. The granular material, on the other hand, gives a negative reaction to the Feulgen test, but after exposure to periodic acid and Schiff's reagent it turns brilliant red. The occasional large deeply basophilic concretions within or adjacent to giant cells in old granulomas (fig. 3, *B*) react positively to von Kossa's stain and negatively to the Prussian blue stain. In the present series concretions were present in some cases in which extravasation had occurred 2 or 3 years before the lesions were examined.

Unaltered sperm were present for at least a year after injury in case 2. Sperm may have persisted in the interstitial spaces for several years in case 3, but the occurrence of another extravasation cannot be excluded.

DIAGNOSIS

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COMMENT

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[4] Simeone, F. A. and Young, W. C.: A study of the function of the epididymis. J. Exp. Biol., 7: 163–175, 1930–1.

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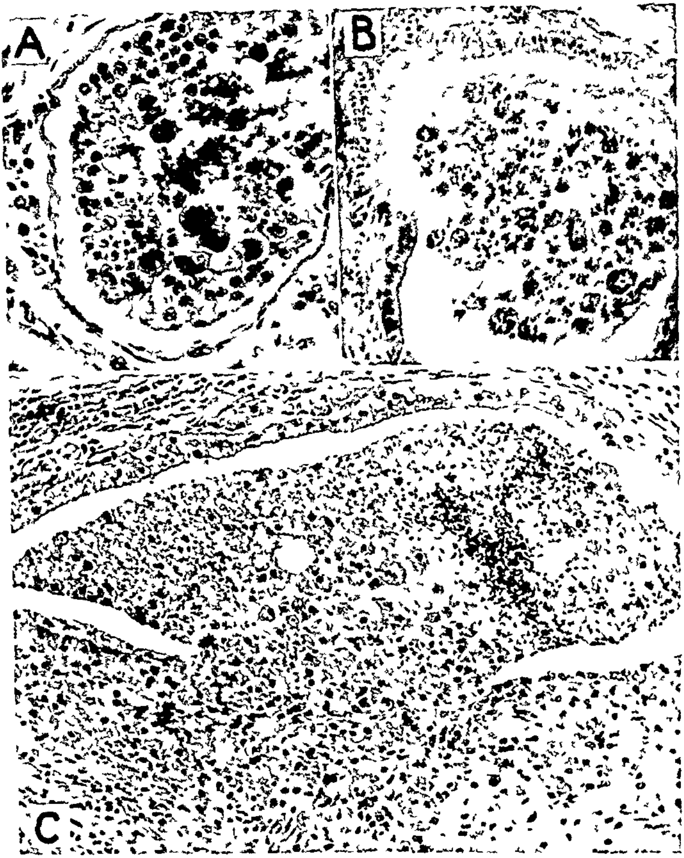

Fig 4 *A*, (negative 100421, AIP 100915) Multinucleated spermatic elements in seminiferous tubules are to be distinguished from spermiophages, *B* × 275

B, (negative 99750, AIP 183709) Macrophages laden with sperm in ducts of epididymis × 185

C, (*negative 102360, AIP 191220*) Pigment laden macrophages surround and fill a tubule of a dilated epididymis congested with sperm × 210

The relatively low temperature of the scrotum may affect the course and character of an inflammatory reaction in the testis and epididymis and *may* be responsible, at least in part, for some features of spermatic granuloma and granmay provide data which will make possible new experimental attacks on the problems of fertility and the biology of the male gamete.

SUMMARY

A series of granulomas which formed subsequent to extravasation of sperm have been studied at the Army Institute of Pathology. Most of them followed surgical procedures on or trauma to the genital ducts. From a practical viewpoint, spermatic granulomas are important because they simulate other lesions, particularly tuberculous epididymitis, even histologically. The factors leading to the development of spermatic granulomas and the granulomas encountered in certain types of orchitis are not clearly understood. Possibly the specialized chemical characteristics of the nucleoproteins of germ cells are responsible for some of the unusual features of the granulomatous reactions. Important information has been gained from investigation of inflammatory reactions involving sperm, and it seems clear that further histologic studies of this biologically unique material might shed light on the subject of human fertility and related problems.

ACKNOWLEDGEMENT

The material on which this study is based was contributed to the Army Institute of Pathology by Drs. I. Imber, S. W. Holley, I. Madoff, T. L. Chiffelle, W. Hamblin, W. B. Spickard, A. Steer, G. T. Joyce, J. B. Frerichs, R. L. Hullinghorst, E. Baron, L. C. Milstead, and J. R. Carter, from the Halloran, Fitzsimmons, Gardiner, Bruns, McCaw, Murphy, Valley Forge and Letterman General Hospitals, Kecoughtan Veterans' Hospital, Fourth Medical Laboratory, Antilles Medical Laboratory, Fort Bragg Station Hospital and National Nava Medical Center; and by Dr. H. H. Leffler of the Providence Hospital and Dr. L L. Blum of Terre Haute.

The photographs were all prepared by Mr. Roy Reeve.

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FATAL EMBOLISM FOLLOWING URETHROGRAPHY

HOWARD GAUDIN

Crabtree has directed attention to the dangers of embolic accidents in the performance of urethrography. Experience with one contrast medium, as set out below, has led to the abandonment of this medium in such studies.

A man aged 61 complained of difficulty and frequency of micturition. He denied past venereal infection, and claimed that his troubles started when he was hospitalized in 1944 for the repair of a right inguinal hernia. Following the operation he had had to be catheterized on a number of occasions, and he stated that difficulty was encountered, requiring the use of a metal catheter.

On examination 2 years after this operation, the patient presented a story of easy fatigue, some shortness of breath on exertion, and urinary difficulty. The heart was not enlarged, the blood pressure was 160/110. The external genitals were normal, the prostate not enlarged, and the urine, both chemically and microscopically, normal. An attempt was made to pass a soft rubber catheter, and an obstruction felt in the region of the triangular ligament. A single woven gum elastic filiform passed easily into the bladder, but a 12 F following bougie was gripped at the same point in the posterior urethra, as already demonstrated. There was no bleeding from the urethra, nor did the patient suffer any pain at the time of this preliminary examination.

With the idea of obtaining more information about this stricture before proceeding with treatment, it was decided to make a urethrogram, and this examination was conducted 3 days later. The patient remarked no untoward symptoms in the intervening period. The method employed had been routine over the past 5 years, and had given uniformly good results in some hundreds of cases (Gaudin). The apparatus for making the injection included an air reservoir in which pressure was maintained by means of an ordinary sphygmomanometer bulb. This was connected to a mercury manometer and to the barrel of a large glass dressing syringe used to contain the contrast medium. From this reservoir the injection was made through a Janet nozzle held against the urethral meatus. This apparatus was described by Kohnstam and Cave. The contrast medium was a 40 per cent suspension of barium in a ½ per cent gum acacia solution in water.

It is recorded that the medium flowed easily, the pressure recorded being below that usually noted (100 mm. Hg). The exposure was made while the medium was flowing. The patient appeared quite comfortable, and about 10 minutes later stood down from the table. He then complained of dizziness and the attendant thought he was going to faint. The heart stopped about 10 minutes after the original injection, although spontaneous respirations continued for some few minutes longer.

The x-ray film exposed at the time of making the injection showed the contrast medium already throughout the cavernous bodies, the corpus spongiosum at least, and through the veins of the pelvis. Postmortem x-rays showed the medium ascending in the iliac veins and the inferior vena cava.

At autopsy an old false passage could be demonstrated on the right wall of the urethra 1 inch distal to a dense small caliber stricture. This was the mode of entry of the contrast medium to the vascular system. The prostate was normal and the bladder moderately trabeculated. Barium could be demonstrated in the coronary arteries, and it is believed that this man died as a result of the coronary embolism.

Accidents of this nature and complicating retrograde urethrograms must be very uncommon. The "urethrogram" is so striking that it cannot fail to impress the examiner. Grossmann (1946), reporting on pulmonary oil embolism, cites 2 further cases following hystero-salpingography and quotes 13 further cases of oil embolism complicating this type of examination. He also cites cases of fat embolism following oil distension of the urethra to facilitate instrumentation (Patterson 1931, and Carr and Johnson 1935). As a complication of urthrography are cited 3 cases by Kohnert (1939) and one case by Eichler (1932).

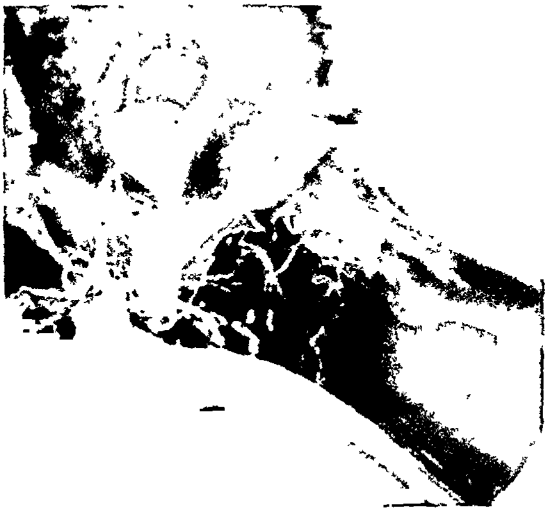

Fig. 1

The earliest urethrographic studies were made by Cunningham in 1910 and there have been a large number of contrast media employed by various workers. The problem is to secure adequate opacity to give good contrast in a particularly dense part of the anatomy. Lipiodol and the barium suspensions we employ have been very successful in this respect, but they both present obvious dangers if they should enter the venous system. It would seem self-evident, therefore, to employ some medium that, should the rare accident occur of its entry into the blood-stream, it could cause no danger to the patient. Hippuran and the materials commonly used for excretion urography give adequate shadows. The patient is then protected from the dangers described above, although these substances, we should realise, still may have unpleasant sequelae should extravasation into the tissues occur.

SUMMARY

A case of fatal embolism from the entry of barium into the circulation in the course of the examination by urethrogram is described. A short review of fat em-

bolism complicating urethrography is given The problem of contrast medium for this examination is discussed

41 Symonds St , Auckland, New Zealand

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large bulb catheter in place. It shows the Albarran elevator depressing the catheter to a rather acute angle which may occasionally be necessary for the engagement of the tip in the ureteral orifice. After engagement of the tip the elevator is released and the catheter then has a more or less straight course up to the kidney.

The single disadvantage of the instrument to date has been the fact that the sheath is necessarily of 28 F caliber. The passage of the 28 F sheath through the unanesthetized male urethra may be painful and usually requires anesthesia. For use in the female this cystoscope has presented no difficulties and the writer sees no further indication for the use of the air cystoscopy.

CONCLUSIONS

A new type cystoscope for the purposes of dilating and calibrating ureters and the passage of stone extraction instruments has been presented. It is believed that this cystoscope has distinct advantages over air cystoscopy methods, as well as over the present standard water cystoscopes when used for the above purposes. It is a modified cystoscope using the principles of pre-existing instruments such as the McCarthy lens system and the Albarran elevator.

The writer expresses his sincere thanks to Mr. Frederick J. Wallace of the American Cystoscope Makers, Inc., who so kindly constructed this instrument.

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A COMPLETELY ROTATABLE RESECTOSCOPE

FREDERIC E B FOLEY

INTRODUCTION

All present endothermal resectoscopes are modifications of the original resectoscope described by Maximillian Stern in 1926

The numerous modifications and improvements of Stern's instrument are too numerous and intricate to warrant detailed description and reference here They have tremendously enhanced Stern's conception and have made possible endothermal transurethral prostatectomy as we see it today

In the original Stern instrument, and in all modifications of it until 1939, the lines—high frequency cord, lamp cord, irrigation tube—have had fixed position attachments to the instrument Accordingly, as the instrument—sheath and working element— is turned around the circumference of the vesical neck and prostatic urethra, the lines must turn with it and thus wrap around the proximal end of the instrument This fixed position relationship between the instrument and the lines attaching to it causes much inconvenience, awkwardness and impairment of facility which the resectoscope otherwise possesses In addition to the inconvenience and impairment made by the lines wrapping around the instrument is the confusion made by the changed position of the loop operating lever (Stern-McCarthy) or thumb rest (Nesbit) occasioned by turning the instrument around the whole circumference as required by the operation The operator must keep constantly aware of the changing position of the loop moving element or "fish" for it

In 1939 Wilinsky suggested a design for a "rotating"[1] resectoscope in which the sheath and working element are "rotatable" within a member to which the lines attach This arrangement permitted the lines to remain in fixed position while the instrument was turned around the circumference of the vesical neck as required in the operation for transurethral prostatectomy

The Wilinsky design provided for rotation of about 300 degrees in either direction from a fixed starting point Rotation of the instrument (with reference to the fixed position of the line attachments) across the starting point was not provided and accordingly it could not be rotated continuously 360 degrees and beyond in either direction independently of the fixed position of the lines The Wilinsky instrument has not been made available and the writer knows of no publication describing it

Scott recently improved upon the Wilinsky design with a resectoscope containing a well conceived fundamental design providing a sheath and working element continuously rotatable in either direction without limitation of any starting point, while the lines and their attachments always remain in fixed position This instrument, completely perfected by the American Cystoscope Makers Inc , is available

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[1] "Rotating" is not properly descriptive "Rotatable" is more so The sheath and working element do not "rotate" in performing their function they are rotated—are rotatable—with reference to the fixed position of lamp cord, high frequency cord and irrigating tube attachments into position for performing their function

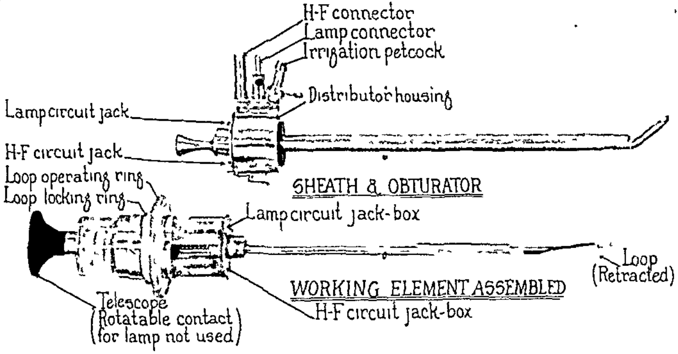

FIG. 2 Foley rotatable resectoscope. Sheath is shown with obturator in place and working element is assembled w
Means of completing high f to working element via jacks and jack-boxes when parent.

This provision of line attachments to the working element is present in all standard endothermal resectoscopes with or without the rotable feature.

From extensive inquiry it appears that few, if any, experienced operators actually make use of the working element water connection. Instead they connect the water tube to the stand pipe on the sheath with petcock interposed. This latter arrangement permits filling and emptying the bladder without need of placing the working element in the sheath. In this way rapid filling and emptying—as during evacuation of resected pieces and use of observing telescopes—is permitted without use of the working element or need to transfer the water connection from the working element to the sheath.

To preserve fully the prime purpose of the Wilinsky and Scott instruments the water line must go to the rotatable connector on the working element and advantage cannot be taken of bringing the irrigating stream to the sheath. Berry recently suggested a new rotatable water connection on the sheath, which somewhat undoes this disadvantage of the Wilinsky and Scott instruments. It permits the water tube connected to the sheath to remain stationary as the sheath and working element are turned around the circumference.

The presently available Scott instrument with its cumbersome pistol grip, though nicely designed and beautifully made, seems not to be the complete answer to the wish for a completely rotatable resectoscope.

In all resectoscopes—rotatable and otherwise—the line connections to the working element are in many ways not desirable. When the working element is set aside to permit use of an observing telescope or the tissue evacuator, either the lines must be disconnected or the element must be set down in close proximity—usually on the patient's lower abdomen.

From the foregoing comments concerning presently available resectoscopes, it appears desirable to have a resectsoscope embodying the following:

1. The instrument itself—sheath and working element—continuously rota-

table in either direction without limitation and independently of the lines which remain in fixed position.

2. All line attachments to the sheath with no attachments to the working element.

The desiderata mentioned above appear to be provided in a satisfactorily functioning new resectoscope here described and illustrated.

The instrument illustrated was fabricated by the writer and his talented and skillful co-worker, Mr. J. Russell Hallman, except for certain standard parts (sheath, loop, telescope, obturator, petcock, lamp and high frequency terminals) supplied by American Cystoscope Makers, Inc. and an improved loop locking device designed and made by Messrs. Frederick J. Wallace and Joseph Held (of American Cystoscope Makers, Inc.) who have given unstinted assistance and cooperation.

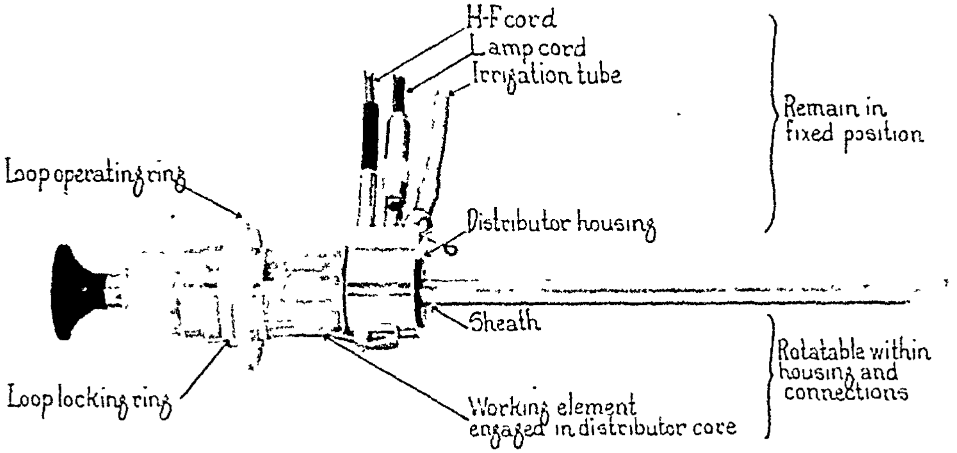

FIG. 3. Foley rotatable resectoscope. Working element is in place in sheath and distributor. Lines—high frequency cord, lamp cord and water tube—have been connected. Fenestration of sheath and loop are directed toward 6 o'clock position.

DESCRIPTION

Affixed to and carried by the proximal end of the sheath is a "distributor" through which the irrigating stream is conducted to the sheath lumen and the lamp and high frequency circuits are conducted to the working element—when it is placed in the sheath.

The distributor is made of a "distributor core" (of insulating material) affixed to the sheath and a "distributor housing" made of metal surrounding the core. The sheath and distributor core affixed to it are entirely separate from the distributor housing and are rotatable in the housing like an axle in its hub. The lamp and high frequency circuit terminals and water tube petcock are carried by the housing which remains always in fixed position, while the sheath with working element in place may be rotated without limitation in either direction.

The water enters the sheath lumen through a passageway of design almost identical with Berry's rotatable water connection but made as an integral part of the distributor. The lamp and high frequency terminals carried by the distributor housing have brushes or shoes which make contact with and ride upon collector rings carried by the rotatable distributor core From these collector rings pins (jacks) project from the proximal face of the distributor core to be engaged by corresponding receptacles (jack boxes) carried by the working element—when it is placed in the sheath

Within the working element structure (barrel) the lamp and high frequency circuits are completed by conductors going from the respective jack boxes to the lamp and to the loop

The loop is projected by forward movement of the operating ring which extends around the whole circumference of the working element barrel and may be operated by thumb or finger pressure at any point on its circumference Accordingly the loop moving element is always available for thumb or finger pressure at any point on the circumference and there is never need to "fish" for it Forward movement of the loop compresses a spring Release of the compressed spring effects loop retraction in a way identical with the Nesbit resectoscope mechanism

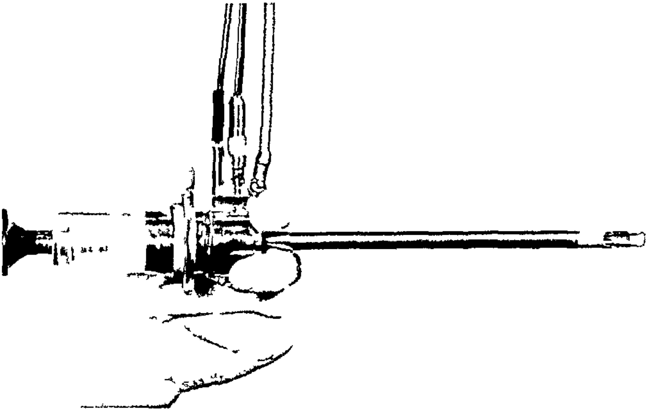

FIG 4 Foley rotatable resectoscope Instrument is shown in operator's left hand, in accordance with writer's way of handling it The fenestration of the sheath has been rotated around to 2 o'clock position By thumb pressure on loop operating ring, loop has been almost fully projected Compare position of sheath fenestration and loop with that shown in figure 3 Note that despite rotation of fenestration, loop and working element to 3 o'clock position line attachments remain in their original position extending vertically upward from their connections on the distributor housing at 12 o'clock position With instrument thus gripped, support of instrument and movement of loop are a one handed operation Opposite hand is free for rectal counterpressure or rotation of working element and sheath into a new position

The instrument as described above is illustrated in figures 1, 2, 3 and 4

COMMENT

The new instrument, as described and illustrated, provides for the first time a completely rotatable resectoscope with all lines remaining in fixed stationary position and attached to the sheath and working element removable from the sheath without encumberance of attached lamp cord, high frequency cord or water tube. These features are prima facie improvement and advantage.

The new and distinctive features and provisions of the instrument have been incorporated with standard A.C.M.I. resectoscope parts and construction and fully preserve the fundamental function of the standard endothermal resectoscope.

Facility in the use of a new device, tool, machine, or surgical instrument of design and operation differing from those long familiar and constantly used, requires adaptability on the part of the operator. The longer a tool is used the more its operation becomes "second nature". Only the adaptable worker will forego the facility of "second nature" operation to lay down the old and take up the new and improved. Once that is done operation of the new device soon comes to be "second nature" too, and its advantages materialize.

In the writer's hands the strangeness of the new instrument rapidly disappeared with continuing use and its operation is now approaching "second nature". With acquirement of this facility the advantages of the instrument have become more and more apparent.

With the sheath and distributor held between the index and second finger of one hand (fig. 4) and the thumb of the same hand resting on the loop operating ring, the loop may be operated indefinitely without requiring a change of grip and without need to "fish" for the loop moving element as the instrument is rotated into new positions. Holding the instrument and moving the loop is entirely a one hand operation, leaving the opposite hand free for intra-rectal pressure of tissue into the loop path. The proximal end of the working element barrel gripped by the thumb and index finger of the opposite hand may be rotated in either direction without limitation. With the distributor and its line attachments remaining in fixed position operation of the instrument and its rotation to any position on the circumference may be continued indefinitely without the nuisance and impediment of lines wrapping about the working element.

During use of the evacuator to remove resected tissue or during use of an observing telescope the working element unencumbered by any line attachments whatsoever may be removed from the sheath and set aside at a distance.

This new form of completely rotatable resectoscope has been in routine use for several months. During this period Mr. Wallace and Mr. Held of American Cytoscope Makers, Inc. have given invaluable aid in correcting faults of design and construction inevitably encountered in a new and intricate instrument of this sort. With their invaluable help, the device has been brought to a stage promising it a permanent place in the field of transurethral prostatectomy.

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MANAGEMENT OF CATHETER DRAINAGE

WESTON T. BUDDINGTON AND ROGER C. GRAVES

For many patients who are undergoing medical or surgical treatment, constant urinary drainage by either the urethral or suprapubic route frequently becomes necessary. Patients with cerebro-vascular accidents who cannot void or are incontinent, and those with acute retention after abdominal operations are familiar examples. Most of these patients, when seen initially, have sterile urine which, after 2 to 6 days of catheter drainage, changes from a sparkling clear product to a cloudy one with pus in the sediment and a positive culture. This latter sequence of events has been seen so frequently that it had come to be accepted almost as inevitable. Is it necessary that such infection take place? From whence do the bacteria come? And finally, is there anything we can do to prevent or delay the invasion of these organisms?

We have sought some of the answers to these questions through a study of 68 patients who have been hospitalized during the past 2 years at the Carney and New England Deaconess Hospitals. The majority of these individuals suffered from some form of prostatic obstruction, although a few had diverticula and calculi as related complications. With rare exception the members of the group fell in the sixth and seventh decades of life and all were males. It is readily apparent that any factors affecting the development of catheter infection will have full play in this class of patients due to the long periods of drainage involved, the instrumentation required and the frequent necessity for bladder irrigations.

Forty-one of these individuals had sterile urines when first seen, but later acquired infection, while 27 had positive cultures at the time they came under our care. The type of procedure carried out in these patients is shown in table 1.

Several patients in the group who were infected when first seen required urological assistance because of bladder retention and infection complicating general surgical procedures.

The pathology of the series is shown in table 2.

Table 3 lists the types of bacteria found in the two groups.

All patients in the series had at least 2 urinary cultures, most of them had more (several cultures were also taken on equipment, urethral secretions, granulation tissue of sinuses, etc.). The urine for culture was usually obtained by aspiration of the drainage tube with a sterile 10 cc syringe and needle after preparing a section of it with tincture of iodine. The bacteriology was determined by the hospital laboratories, and we believe represents a fair cross section of the organisms now commonly encountered.

In this connection it should be noted that the infections were generally mixed (i.e. not due to a single organism) and not infrequently in the early cases as many as 3 or 4 separate species would be recovered from a patient during a 4–6 weeks period of drainage. The question of whether a staphylococcus or streptococcus represented a contaminant or not was at times difficult to assess. We have included them as infections when there was pus in the urine, when another species was present or when the culture was repeatedly positive for these forms.

Accurate determination of some of the organisms is often a matter of considerable experience, skill and persistence. "Running them through the sugars" is frequently only the beginning of a hard problem. The character of bacteria change with media and environmental factors so that their exact identification is frequently extremely difficult for even well trained and alert technicians. The high incidence of Pyocyaneous (Pseud. aerug.) is probably even greater than noted, for the production of greenish-blue pigment is the chief criterion for

TABLE 1. *Type of operation*

	CASES
Two-stage suprapubic prostatectomy	26
Two-stage transurethral prostatectomy	8
Two-stage perineal prostatectomy	1
One-stage suprapubic prostatectomy	4
One-stage perineal prostatectomy	8
One-stage transurethral prostatectomy	15
One-stage suprapubic cystotomy	1
Catheter drainage only	5
Total	68

TABLE 2. *Pathology of obstruction*

	CASES
Benign hyperplasia of prostate	26
Benign hyperplasia of prostate with infection	29
Carcinoma of prostate	7
Fibrosis bladder neck (with contracture, atony)	6
Total	68

TABLE 3. *Types of bacteria recovered*

	TOTAL CASES	
	41	27
Esch. coli	17 (41%)	20 (73%)
Pseud. aerug	23 (56%)	13 (48%)
Aerob. aerog	12 (29%)	9 (33⅓%)
Proteus	5 (12%)	5 (18%)
Enterococci	8 (19%)	10 (36%)
Streptococci		
Hemolytic	3 (7%)	3 (7%)
Anhemolytic	10 (24%)	3 (7%)
Staphylococci	10 (24%)	5 (18%)
Paracolon bacillus	2 (4%)	1 (3.7%)

its identification, but Stanley of the Massachusetts Memorial Hospital states that these organisms may also produce yellow pigment or none at all. As this is one of the most common and persistent invaders we now have to deal with, knowledge of its presence is essential to planning suitable therapy.

To provide a base line with which to compare our results we have assumed from past experience that patients placed on catheter drainage of the conventional type in the average hospital acquire infection at least to the bladder level by the end of the first week, often earlier. This takes place in spite of drugs and forced fluids as in the following cases (table 4), which we submit as typical examples.

What are the factors responsible for infection in this group of patients? Although we do not doubt that the etiology must include such possibilities as a) reactivation of a latent process in the prostate and urethra, b) blood and lymph borne invasion of the bladder, and c) retrograde extension of infection along catheters, nevertheless, we believe that mechanical introduction of bacteria is more frequently to blame. This we should be able to control.

TABLE 4. *Patients developing early infection*

BACTERIA RECOVERED	DAY OF CATHETER DRAINAGE
Case 1. Pseud. aerug.	5
Case 2. Enterococcus Aerob. aerog. Esch. coli	4
Case 3. Staph. alb.	5
Case 4. Esch. coli Enterococcus Pseud. aerug.	6

In the first place, sterilization of the catheter, forceps, instruments, syringes, glass connections, basins, irrigating solutions, rubber tubing, drainage bottle, gauze, lubricant, etc., must be absolute. Secondly, meticulous attention to preparation of the external genitals or operative site is essential. Any break in the above chain will result in the introduction of bacteria at the time of initial instrumentation or of subsequent procedures. For example, failure to protect the open end of the catheter and glass connection from contamination when bladder irrigations are performed is a common incident of careless technique. Finally, we have come to insist not only on sterility of the drainage tubing and bottle, but also that the latter be provided with a cork pierced by two glass connections to one of which the drainage tube is attached, while the other acts as an air vent (fig. 1).

This entire outfit of bottle, cork, tubing and connections is wrapped and autoclaved intact, thus coming to the patient's bedside secure from contamination.

Such a drainage system has two advantages. It prevents the reverse siphonage of bottle contents when the latter is raised above the bladder level as is so frequently done by both nurse and patient. It also protects the lower end of the drainage tubing from gross contamination by a pool of infected urine, in case reflux from the tube does occur. We have adopted a schedule of replacement of the sterile tubing and bottle every other day.

Before the institution of this system of drainage we cultured simultaneously many urines both at the bladder and drainage bottle levels. Positive cultures were generally obtained from the bottle first and from the catheter at a later date, occasionally both became positive on the same date, as one might expect. The species isolated in the separate specimens were almost always identical. When urine for culture was taken from the lower end of the tubing just before it entered the bottle positive reports were much less common than from the bottle contents, implying we believe, that the latter is a most fertile source of innoculum. Tables 5, 6 and 7 are examples taken from the series.

Table 8 illustrates the ineffectiveness of chemotherapy alone in preventing infection in patients on catheter drainage. The bacteria listed were recovered from the bladder urine while the patients were receiving the drugs as noted, in accepted therapeutic doses.

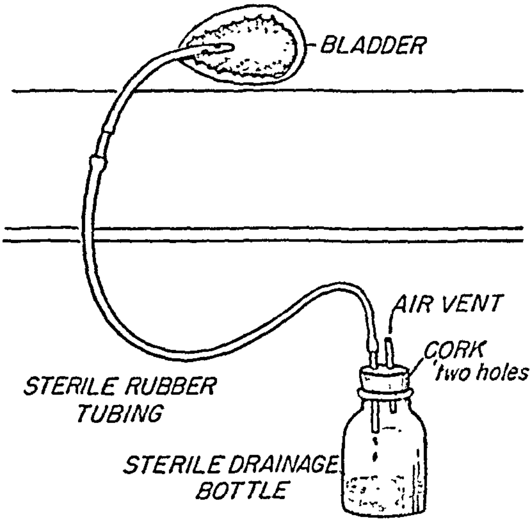

FIG. 1

There are strains of all these bacteria which are resistant, or readily become resistant to the urinary antiseptics, since patients on catheter drainage frequently develop infection during the administration of these drugs. It is unsatisfactory to depend upon drugs alone without the sterile precautions that we have emphasized but we commonly use the sulfonamides or the antibiotics, or both, for the control of infection or to lessen the likelihood of its occurrence. Continuous medication at regular intervals, at night as well as during the day, offers the greatest protection as far as drugs are concerned; interruption of the program for a number of hours may allow the bacteria a foothold from which it is difficult to dislodge them. In the case of mixed infections a combination of drugs must be used since removal of one bacterial strain may permit another to flourish as has been shown by several observers.

Streptomycin was employed in 10 individuals for serious infection due to gram negative bacilli, especially Proteus and Pseudomonas, and for protection of poor risk patients. Due to its lower cost and lessened toxicity in the smaller doses now found generally effective, we are administering it not infrequently for terminal disinfection prior to discharge from the hospital.

TABLE 5. *D. F., aged 80*

DAYS OF CATHETER	URINE CULTURE, BOTTLE	URINE CULTURE, CATHETER
5	Staph. alb.	No growth
6 Transurethral resection of prostate		
7		No growth
8	Pseud. aerug.	No growth
10	Pseud. aerug.	Pseud. aerug.

TABLE 6. *A. B., aged 80*

DAYS OF CATHETER	URINE CULTURE, BOTTLE	URINE CULTURE, CATHETER
4 Suprapubic cystostomy		No growth
10	No growth	No growth
19 Prostatectomy		
21	No growth	No growth
23	Aerob. aerog.	Aerob. aerog.
26	Aerob. aerog.	Aerob. aerog.
35	Aerob. aerog.	Aerob. aerog.

TABLE 7. *F. K., aged 75*

DAYS OF CATHETER	URINE CULTURE, BOTTLE	URINE CULTURE, CATHETER
1 Cystotomy		
3	No growth	No growth
6	Pseud. aerug.	No growth
9	No growth	No growth
10	Pseud. aerug.	Pseud. aerug.
19 (receiving streptomycin)	No growth	No growth
20 Prostatectomy		
27	Pseud. aerug.	Pseud. aerug.

TABLE 8. *Infection developing during chemotherapy*

DRUG	BACTERIA
Case 1. Sulfadiazine	Pseud. aerug.
Case 2. Sulfiadiazine	Pseud. aerug. Non-hemol. streptococcus
Case 3. Sulfadiazine	Esch. coli
Mandelic acid	Streptococcus
Mandelic acid	Pseud. aerug.
Case 4. Sulfadiazine and penicillin	Esch. coli, enterococci and streptococcus
Case 5. Sulfadiazine	Proteus
Sulfadiazine and penicillin	Aerob. aerog. and non-hemol. streptococcus

Table 9 presents in brief some of the results of our efforts to combine the sterile treatment of drainage with chemotherapy in recent cases. The periods were determined from the first day of catheter drainage to the last date with a sterile

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A DEVICE FOR REMOVING CLOTS FROM THE BLADDER; A NEW IRRIGATING NOZZLE

GIDEON TIMBERLAKE

As I have previously stated, no operative procedure ever evoked more fantastic claims of success at its inception than did that of transurethral prostatic resection. For a while, it was the fashion for every one who could buy the implements to go at the procedure with hardly more than a scant knowledge of the technique, the hazards, heartaches or the real grandeur of the method. Tomes have been written about the good results, little about the not infrequent complications such as ruptured bladder, injured sphincter, recto-urethral fistulas, incontinence, postoperative hemorrhage, and just plain deaths.

Having been one of the pioneers of endourethral surgery, I have seen just about every phase, good and bad, and particularly the annoying hemorrhage during and after surgery, sometimes as long as 3 weeks later. I am especially concerned in this offering with secondary hemorrhage in which fused aggregations of clots form to present rather difficult problems. In this regard, of considerable importance is the fact that, as seen by me and confirmed by many observers, there is nothing that keeps a bleeder bleeding like blood clots. Further, no satisfactory explanation has been given for this phenomenon. I have concluded that, in the process of clotting, threads of fibrin become attached to margins of the blood vessels and as they contract, simply prevent the mouths of the vessels from closing. To support this conclusion, upon removing the clots many hemorrhages cease. If the bleeding does not cease of this procedure, we have at least cleared the field for fulgurating the offending areas.

I have used practically every device for removing clots from the bladder. Many have been clumsy and inadequate. It is reasonably simple to introduce a resectoscope or panendoscope sheath through which the clots may be aspirated by the Ellik, Toomey or other evacuating syringes. But, regardless of the demand for getting the clots out, these fused masses have to be disintegrated before satisfactory removal can be accomplished. I still have great confidence in the old time glass asbestos plungered syringe. But for breaking up clots I have a simple method to offer, both for the various sheaths and the special instrument which is later described. By use of the aforementioned sheaths I often find that the bladder lining becomes engaged when I have to release it by forward pressure from without.

Several years ago I hit upon a plan for removing clots, whether the patient is on operating table or on a bed pan, when all the work can be easily carried on. A description follows:

The device is fashioned somewhat like the letter S with the amplitudes of the curves very shallow. The diameter is that of 26 F; 30 cm. in length. The device is introduced by a steel-ribbon obturator which has a bouled tip. Just behind the distal end there are four elliptical fenestrae designed to prevent incorporating the bladder mucosa. These measure 5 by 7 mm.

The proximal end of the "declotter" has a female adapter socket which accepts the Ellik evacuator or the Toomey syringe (fig. 1). To further assist me I have the male adapter inserted into a sturdy piece of red rubber hose so that it may be used with any sort of syringe and through which irrigations may be given

I previously have mentioned the necessity for breaking up fused clots, it can be easily accomplished by a very simple device, that of bending a piece of tonsil wire upon itself of such length as will permit it to extend about 2 or 3 cm beyond its mouth Then we grasp the proximal portion with a clamp and begin a rotary movement as we move tip from side to side very cautiously One urologist suggested that I include a water conduit That is avoided because the cannula will permit a 14 or 16 straight catheter to be passed into bladder whenever irrigations are indicated Further, the kidneys are supposed to furnish some of the fluid The name of this device is the "declotting cannula "

Since I have been in the practice of urology, one of my greatest concerns has been that of owning and enjoying an irrigating nozzle for urethral catheters that would not break into bits when it hit the floor Over the years irrigating nozzles have been made of glass, clumsy and inefficient I believe that now I have one which will serve many purposes and serve them well (fig 2) I hereby offer an all service irrigating nozzle made of metal that is boilable and bounces well It can be used for tube connections, irrigating urethras or catheters, dilating the urinary meatus It carries a Luer adapter at the proximal end into which a glass syringe may be inserted for filling bags of retention catheters Its dimensions are length, 6 cm , shoulder to apex, 4 cm , diameter at apex, 4 mm , base size, 28 F and shoulder, 39 F It has a 2 mm bore

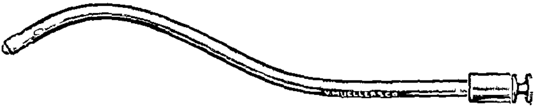

FIG 1

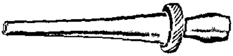

FIG 2

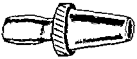

FIG 3

The third issue is that of having a satisfactory nozzle for irrigation through catheters and I have devised one by cutting off the longer nozzle about half-way its length and drilling it to a 4 mm bore through which fluids may run more freely and in greater volume so that time is saved at the work of lavage (fig 3)

SUMMARY

As soon as the "declotter" was exposed for survey and sale at the meeting of the American Urological Association in Buffalo, N Y in 1947, our colleagues came right along and poured in orders well over the hundred mark before I left They all appeared very naive and innocent, had done their penance, and were willing to confess openly that some of them, at some time, had actually seen a blood clot or so during the width of their vast experiences!

The devices described here are manufactured by V Mueller and Co , 408 S. Honore St , Chicago, Ill

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A NEW DEVICE FOR INFLATING AND DEFLATING CATHETER BAGS

GEORGE G. GILBERT

A time and labor saving device, applicable to all types of bag or balloon catheters, will be described. It renders them easier to handle and more practical for both the doctor and the patient.

The device consists of a rubber plug which, during manufacture, is placed in the distal end of the inflating tube and cured with latex. This process insures an air and water-tight union. Inflation and deflation of the bag is then carried out by using an ordinary syringe and needle (fig. 1). The plug is similar to the type commonly seen in bottles containing drugs for parenteral use. Multiple insertions and removals of a needle are then possible without subsequent leakage or contamination.

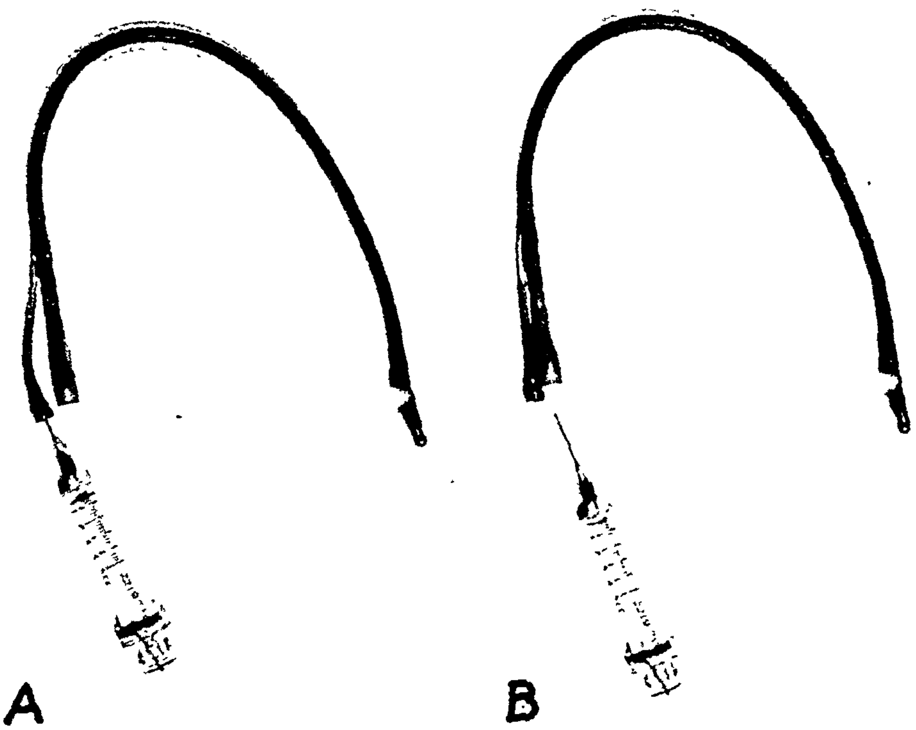

FIG. 1. *A*, syringe, with needle inserted through rubber plug, and bag being inflated. *B*, showing maintenance of inflation after removal of needle.

The advantages are: 1) The clumsy attempts to inflate the bag with an ill-fitting syringe, and the concomitant leaks of fluid are avoided. 2) One can be certain of delivering accurately the desired volume to the bag. 3) There is no necessity to secure the inflating tube with a metal clamp, rubber band, or string. 4) The risk of the inflating tube getting caught as a patient is moved from operating table to stretcher is lessened. 5) There is less chance for the bag to become deflated accidentally.

The practical necessities for the workability of this device are obvious. The union between the plug and the inlet tube must be air- and water-tight, and allow sterilization without losing these qualities. The rubber must be of such a nature that it will allow repeated needle punctures and still seal off completely after withdrawal of the needle.

Samples, manufactured through the kindness of C. R. Bard, Inc., seem to fulfill all the practical criteria. One 5 cc bag catheter was left in a patient for 2 weeks. On removal 4.5 cc was aspirated. The same catheter now has been in another patient 3 weeks, and is still working satisfactorily. A second sample has received approximately 20 injections with a size 22 needle before leaking occurred. The leakage was of scant volume and stopped spontaneously after 10 minutes. A normal catheter certainly would have reached its life span of usefulness before this number of injections had been reached. More experience may indicate the need for further refinements.

SUMMARY

A rubber plug sealed in the distal end of the inflating tube of a bag catheter permits easy inflation and deflation of the bag. The advantages and practical requirements of this device, as well as the author's experience with samples, have been discussed.

409 Flat Iron Bldg., Asheville, N. C.

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TWO MINIATURE URETHRAL CATHETERS

MEREDITH F. CAMPBELL

From the Department of Urology, New York University College of Medicine, New York, N. Y.

The urethral catheter is employed more often in infants and children than a urologic instrument. In this group it is today employed chiefly for the asep collection of specimens when the clinical problem is concerned with urina infection, either known or to be ruled out. Here the specimen should always obtained by catheterization in females of all ages, and also in males from wh one cannot get an aseptically collected voided specimen. Only by employing th method can contamination be avoided, the correct bacteriologic and cellul identification made, and the progress of therapy ascertained. The increasi recognition of the value and necessity of this procedure by both urologists a pediatricians is encouraging. Catheterization is seldom required for the relief acute vesical urinary retention in the young.

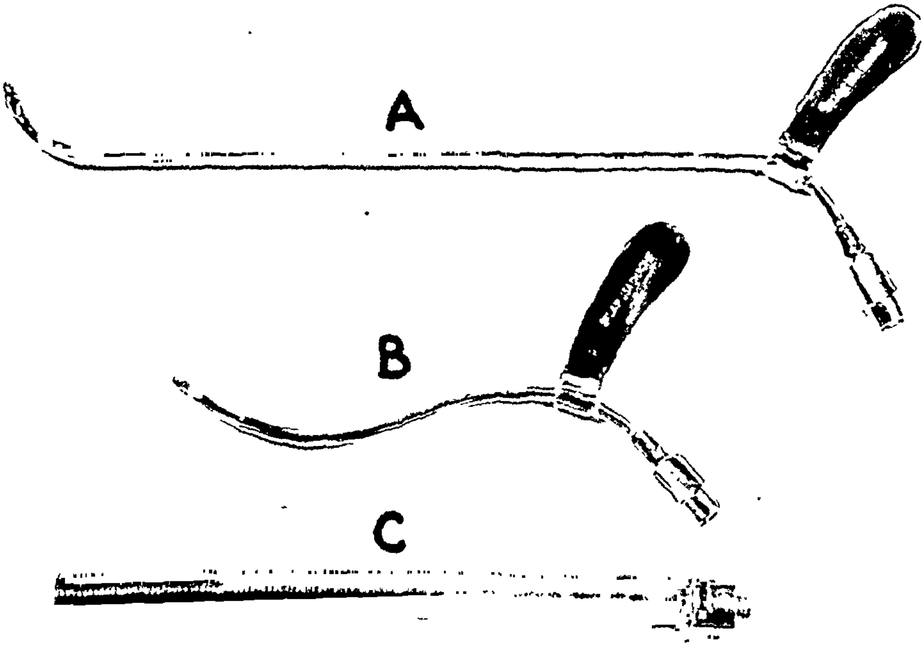

FIG. 1. Campbell miniature catheters. *A*, male catheter. *B*, female catheter with genero fin handle and female Luer connecting tip. *C*, rubber tubing with male Luer connecti fitting.

In order to minimize the technical difficulties of aseptic catheterization children, engendered by behavior problems, lack of cooperation, limited worki space and a small urethral caliber, the writer devised the miniature instrumen shown in figure 1.[1] These catheters of 8 F caliber, noncorrosive metal constructi and adequate length, are notable because of their small size and the genero

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[1] Manufactured by J. Sklar Manufacturing Co., Long Island City, N. Y.

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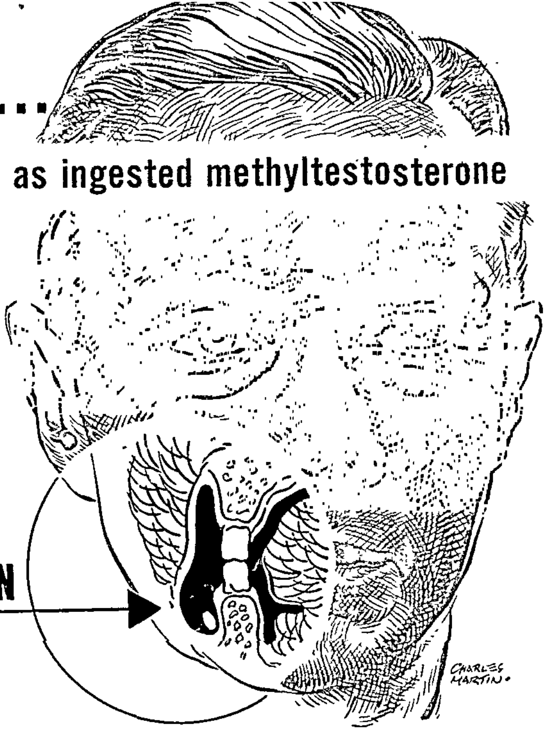

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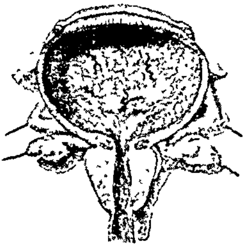

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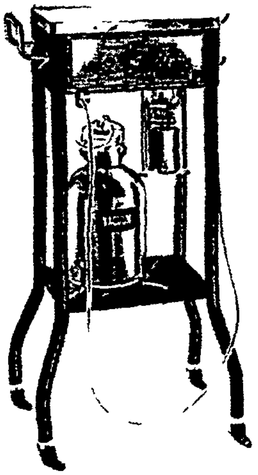

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The Wilmer Institute of which he was Director was created as a tribute by friends and patients Dr Wilmer served as an overseas medical officer during the first World War and was a Brigadier General in the Medical Reserve Corps He was a founder of the American College of Surgeons and contributed much to the literature on ophthalmology

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ETHICON SUTURE LABORATORIES, DIVISION OF JOHNSON & JOHNSON, NEW BRUNSWICK, N

Chicago, Ill.—Photograph in Ethicon Suture Laboratories, showing ribbons of surgical gut being inspected just prior to immersion in chrome bath. After chromicization several ribbons are spun into a completed suture strand. Tru-chromicizing before spinning, an exclusive Ethicon process, assures uniform chrome disposition, resulting in uniform digestion by tissue enzymes.

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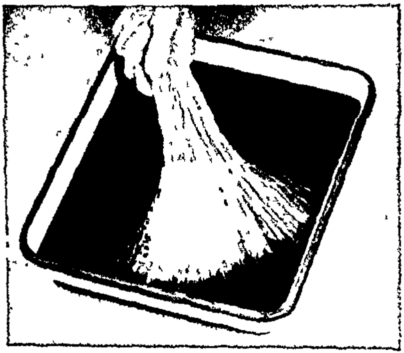

When gut is chromicized after strands are spun and dried, chrome concentration is very high in surface layers and relatively low in the core Inner core is digested rapidly—the highly chromicized periphery survives for prolonged periods

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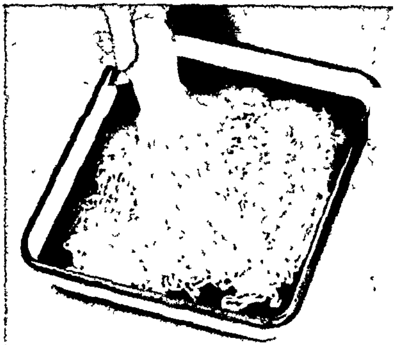

Individual ribbons of gut are soaked in chrome bath befo *they are spun into strand, permitting uniform deposition chrome The strand thus has the same chrome content fro periphery to center.*

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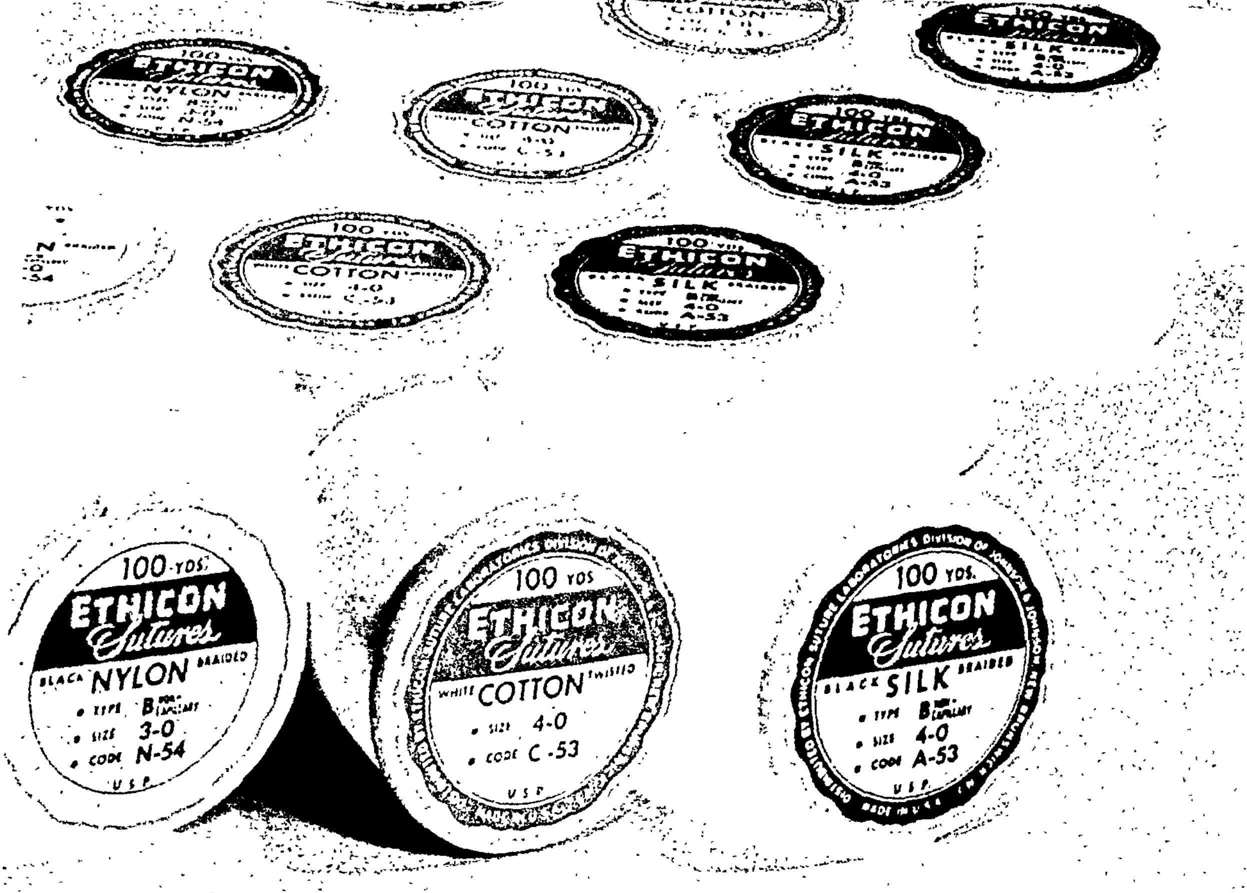
*To illustrate this comparison, small laboratory trays are used. In commercial production, surface-chromicizing is done under tension. *Both processes are performed in large vats.*



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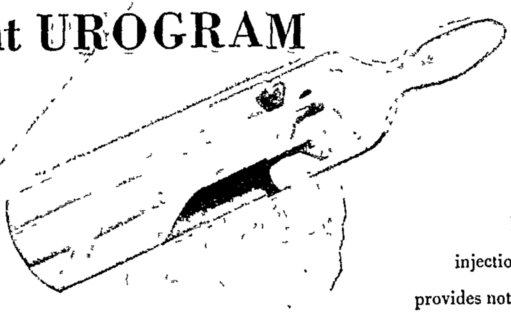

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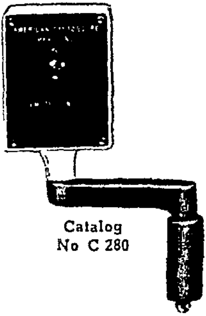

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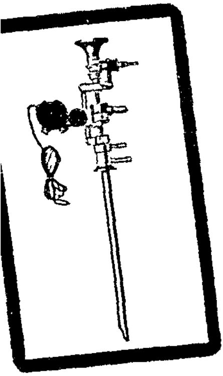

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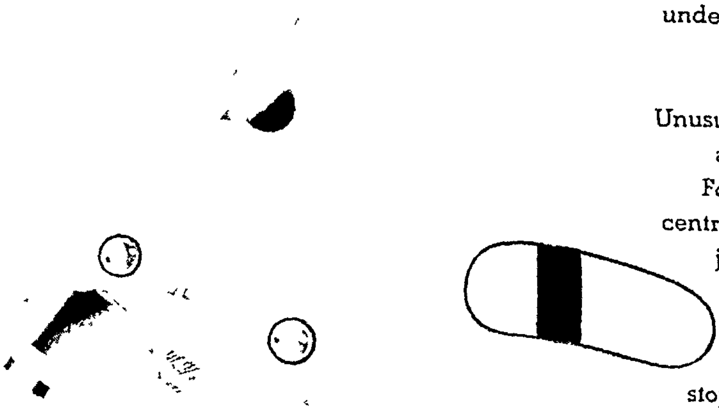

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The Nomenclature Committee requests suggestions concerning additions to the published Urological Nomenclature, and also suggestions concerning changes in the present list of accepted diagnoses. The chairman requests that correspondents send him a carbon copy as well as their original letter to simplify the secretarial problem.

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THE JOURNAL OF UROLOGY
Vol. 62, No. 6, December 1949
Printed in U.S.A.

THE PRESENT ORGANIZATION OF THE AMERICAN UROLOGICAL ASSOCIATION

CHARLES C. HIGGINS[1]

The American Urological Association was organized and the first annual meeting held in Saratoga Springs, New York, in 1902. As the organization has grown, changes in policy, structure and government have been deemed advisable and essential.

The Association's expansion from 350 members in 1907, and 663 in 1925, to 15 honorary members, 11 associate, 26 corresponding, 154 senior and 1112 active members at present, a total membership of 1314, signifies the ever increasing interest in our specialty and the role of urology in modern medicine.

In recent years but few changes have occurred in the administration of the Association. Article 2, section 8 of the by-laws states, "The duty of the Executive Committee shall be: to administer the affairs of the Association."

The Executive Committee consists of the president, president-elect, secretary, treasurer and one member (or his duly elected alternate) from each section for membership on the Executive Committee, this member having been elected by a majority of the Association and his name presented by the nominating committee or from the floor.

Initially there were no branch societies or sections. In 1906 the New York Branch was organized and as membership increased other branches and sections were formed.

In 1940 the 8 present sections were organized as follows: Mid-Atlantic, New York, New England, North Central, South Central, Southeastern, Western and the Central, the name of which this year was changed to the Northeastern Section.

The present membership of the sections are: Mid-Atlantic, 215 members; New York, 289; New England, 179; North Central, 345; South Central, 243; Southeastern 295; Western, 305; and the Northeastern 199 members. The Sections have equal voice in the conduct of the affairs of the Association through their representation on the Executive Committee.

The 5 branch societies of the American Urological Association, namely Chicago, Detroit, Philadelphia, Pittsburgh and St. Louis are not directly represented on the Executive Committee but function indirectly through their respective sections.

In the interim between the annual meetings, the conduct of the affairs of the Association is vested in the hands of the president and secretary. Discussions on policy and other important matters are referred to the Executive Committee for consideration and postal ballot.

The time of the annual session of the Committee is set by the president. The Executive Committee meeting usually takes place on the Sunday preceding the scientific session of the Association. As the affairs of the organization and the reports by the chairmen of the standing committees cannot be adequately considered during one session, additional meetings as requested by the president are in progress daily throughout the meeting. At such times many items are reviewed and discussed such as: examination of the yearly report of the secretary and treasurer; consideration of applications for chartering new branches; presenting recommendations to the Association, and the transaction of any other necessary business not specified in the by-laws.

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[1] Presidential address read at annual meeting, American Urological Association, Los Angeles, Calif., May 18, 1949.

The report of the membership committee is discussed at length and desirable applicants are recommended for election to membership.

Matters of discipline are considered and resignations or reinstatements are approved or disapproved.

The chairmen of the standing committees submit their reports for consideration, discussion and action. Such committee reports as the legislative, membership, editorial and nomenclature are presented by the respective chairmen.

The role of such standing committees is of inestimable value in the conduct of the business and functions of this organization. Duties of committee chairmen continue throughout the year. Considerable time and energy which they expend freely are required in the performance of their difficult tasks. The society owes a debt of gratitude to them.

As our organization has enlarged the obligations of the secretary and treasurer have progressively assumed more importance. Considerable responsibility must be assumed by these officers; cooperation with the other members of the Executive Committee is essential in order that the business of the Association may be carried on in harmony. Our organization has long been fortunate in the selection of these officers.

The financial condition of our association is secure. The Executive Committee believes, and rightly so, that we should continue to accumulate a reserve fund. Many activities and useful purposes requiring appropriations have been necessary in the past and the demands will increase in the future. Careful scrutiny for the disbursement of funds is an obligation of the Executive Committee. Appropriations for activities outside the actual physical requirements of the organization are many and varied. These include the Ramon Guiteras lecture, the Carcinoma Registry and financing the committee on nomenclature of diseases. Disbursements have been considered advisable to stimulate research and interest. This is evidenced in the awarding of certificates and cash prizes for the prize essays, and presentation of the annual award on the human male reproductive tract.

By the use of reserve funds it has been possible to promote the courses of graduate instruction. Other enterprises undoubtedly will be inaugurated in the future.

As might be anticipated, the increase in membership has required the formulation of additional committees. With larger attendance at our annual meetings requests have been made by our members for a scientific exhibit. The Committee on Scientific Exhibits was established in 1933. The late Dr. Nathaniel Rathbun appointed the first such committee which functioned at the meeting in White Sulphur Springs, W. Va., in 1934.

Technical exhibitors became attracted to our annual meeting. In later years the number of scientific and technical exhibits has increased to a point which made it seem advisable to appoint a Director of Exhibits. Mr. William P. Didusch was appointed director in the fall of 1938 and first served in that capacity at the annual meeting at White Sulphur Springs in 1939.

Since that time he has maintained his enthusiasm and his wholehearted cooperation is deeply appreciated by the Executive Committee.

Dr. Samuel A. Vest is to be commended for his untiring interest as chairman of the Committee on Scientific Exhibits. At the present meeting there are 27 scientific and 23 technical exhibits.

The Registry of Genito-Urinary Pathology was established in May 1925. At this time the committee was designated as the Carcinoma Registry Committee (later known as the Tumor Registry Committee). It was appointed as the result of a recommendation by Dr. Herman L. Kretschmer in his presidential address. The original members were: Dr. Herman L. Kretschmer, chairman; Dr. B. S. Barringer, Dr. E. L. Keyes, Dr. George G. Smith and Dr. W. F. Braasch.

In 1925 Dr. Kretschmer stated: "Without fear of contradiction I believe it is fair to state that the most vital problem today, and the one that is no nearer solution, is that which relates to the treatment of carcinoma of the bladder and prostate. It would seem to me to be a move in the right direction for this Association to have a carcinoma registry. To run a register of this sort is no easy matter, but would we not be repaid for the trouble and expense it would entail?" Dr. Kretschmer's dream eventually came true. At the present time we have complete data on 5,641 bladder tumors, 939 kidney tumors, 335 prostate malignancies and 174 tumors of general genito-urinary pathology.

More recently we have been honored by the presence of guests from many countries whom we heartily welcome. In 1941 the Pan-American committee was formed. It is an exceedingly active committee and we hope to maintain and cherish the good will of our Pan-American neighbors.

We are anxious that our foreign guests participate in the discussions during the scientific sessions.

The Committee of Standard Fees (to apply for urological work in contracts negotiated by the Veteran's Administration and various state societies) was founded in 1946. The members of this committee have devoted considerable time to collecting data for consideration by the executive committee.

The Public Relations Committee was appointed in 1946. Many problems arise during the year which are presented by the chairman at the meeting of the Executive Committee. Publicity releases at the time of our annual meeting are supervised by this committee.

In view of comments and publications by individuals of active "anti-vivisective" organizations, we believed it advisable to form a committee on animal experimentation (vivisection). This was accomplished in 1948. We believe that this will be an active group which will perform much constructive work, not only for urologists but for the benefit of the medical profession in general. A report on the role of animal experimentation in scientific medical progress appears on our program this year.

In order to stimulate research, in 1939 the Scientific Research Committee, i.e. the Prize Essay Committee was established. The members are extremely interested in their work and devote considerable time and energy to maintaining the high standards evidenced by the two prize essays presented during our scientific session this year.

The Award Committee for Research in the Human Male Reproductive Tract was formed in 1945. The members consider and discuss possible recipients who merit consideration for the award. Scientific publications are carefully analyzed and the importance of the contributions weighed. The response to the address presented at this meeting confirms the wisdom and excellent judgment of the members of this committee.

The Instrument Collection Committee was appointed by Dr. Oswald S. Lowsley in 1941. It is hoped that members of our Association will cooperate in preserving instruments, many of which may now be obsolete, but will continue to have inestimable historical value.

With the introduction of motion pictures for teaching purposes, the Executive Committee decided that members of our Association would be interested in viewing various surgical procedures. The motion picture committee was selected in 1941 with Dr. Linwood D. Keyser as chairman, and considerable interest and enthusiasm have been since displayed by our members in attending the motion picture sessions. This year the committee has planned the showing of 16 motion pictures.

The Committee on Graduate Instruction was appointed by Dr. Herbert H. Howard in 1949. The interest in our new endeavor is evident by the number of those attending the courses. Although this is our most recent venture, progress is rapid, interest intense and the outlook encouraging.

Without the cooperation of the local arrangements committees the meetings would hardly be a success. Many months are required to plan the necessary details for a successful meeting. Our members deeply appreciate their sincere efforts.

I have presented this brief review to enlighten those, especially the younger members, who are not acquainted with the mechanisms by which our organization functions. The other standing committees are equally as active and important as those I have mentioned which have been established for a longer period of time and you are all familiar with their splendid activities and loyal support.

Those of you who have been unaware of the activities of the various standing committees can hardly appreciate the time and effort necessary to perform the arduous duties of this service to our organization.

The Executive Committee sincerely appreciates their loyal cooperation, enthusiasm and efforts. We are an energetic and progressive organization. The membership is large and a long list of candidates awaits the opportunity to join our number.

To the new members of the Association we extend a hearty welcome. You have been carefully considered by the membership committee We feel you not only have the requisite training to be a member of the American Urological Association, but that you will maintain its traditions May the deeply established friendships that have resulted over a period of years continue to promote harmony and maintain the esprit de corps of this association I should like to reiterate the remarks of Dr George G Smith in his presidential address in 1936 "As a result of my experience while holding this position, I have been profoundly impressed by the serious and conscientious manner in which every member of the governing board has discharged his duties So long as you select such men to conduct the affairs of the Association, its success will be assured "

We have traveled a long way since 1902, and may we continue to preserve and cherish the traditions of our association

Finally, I wish to express my deep appreciation to you for the privilege of having your confidence, and the great honor of your highest office

Cleveland Clinic, Cleveland, O

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PROGNOSIS AFTER NEPHRECTOMY FOR RENAL TUBERCULOSIS

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The use of streptomycin in the treatment of genito-urinary tuberculosis is being extensively studied, and it is possible that after a suitable period of investigation, its use will change our present concepts as to what constitutes "surgical" renal tuberculosis. At the present time some investigators, such as Lattimer[1] and Slotkin,[2] who have had considerable experience with the drug, have suggested certain criteria for the use of streptomycin and for surgery. Thus, when renal tuberculosis is evidenced by unilateral pyelographic changes and positive smears for tubercle bacilli, surgery is indicated. However, in those cases where pyelographic changes are not present, although positive smears are reported, the use of streptomycin without surgery is suggested. Obviously, streptomycin is indicated in any type of bilateral renal tuberculosis. On the other hand, Nesbit[3] states: "It is now evident that we should treat all patients with this disease (urinary tuberculosis) by prolonged sanatorium care and streptomycin therapy whether the infection appears to be clinically bilateral or unilateral. . . . Surgical removal of the grossly diseased kidney is a well accepted principle, but perhaps in the future, nephrectomy can be relegated to a position below that of streptomycin and rest, in order of importance."

At this time, it appears important to add to the literature another series of cases of renal tuberculosis treated surgically and followed for long periods of time to determine the prognosis with surgical treatment. Comparison may subsequently be made with a similar series of cases treated with streptomycin. In the past there have been several papers devoted to prognosis after nephrectomy for "unilateral" renal tuberculosis. The adjective "unilateral" is placed in quotation marks in view of the extensive studies of Medlar[4] which would indicate that renal tuberculosis is always bilateral, at least in its inception. The papers by Wildbolz[5] in 1929, Gile in 1937,[6] Emmett and Kibler in 1938[7] and Nesbit, Keitzer and Lynn[8] in 1945 have all been devoted to this subject. Wildbolz reported 60 per cent of his cases alive after 10 years; Emmett reported 5 year cures ranging from 43.5 to 50.3 per cent; Nesbit reported 50.3 per cent alive 11 years postoperatively. The prognosis was apparently not influenced by age, sex, or the presence of genital lesions in the male. The outlook was adversely influenced, however, by the presence of pulmonary tuberculosis, and more directly by the status of the "good kidney." Thus Emmett reported that if the "good" kidney is free of white blood cells, 43.5 per cent of patients are cured, 65.2 per cent are

[1] Lattimer, J. K., Stearns, W. H., Amberson, J. B., Schwartz, R. G. and East, W.: J. Urol., **60:** 974, 1948.

[2] Slotkin, G. E.: J. Urol., **58:** 464, 1947.

[3] Nesbit, R. M. and Bohne, A. W.: J. A. M. A., **138:** 957, 1948.

[4] Medlar, M.: Am. J. Path., **2:** 401, 1926.

[5] Wildbolz, H.. J. Urol., **21:** 145, 1929.

[6] Gile, H. H.: Surg., Gynec. & Obst., **64:** 1046, 1937.

[7] Emmett, J. L. and Kibler, J. M.: J. A. M. A., **111:** 2351, 1938.

[8] Nesbit, R. M., Keitzer, W. A. and Lynn, J. M.: J. Urol., **54:** 227, 1945.

improved and 20.3 per cent stand a chance of dying in 5 years. If the guinea pig and acid fast smears of the "good" kidney are also negative, 50.3 per cent of patients are cured, 75.2 per cent are improved and only 13.3 per cent stand a chance of death in 5 years. However, if the guinea pig and acid fast stains are contralaterally positive, we may expect a 5 year cure in only 21.8 per cent, whereas 41.8 per cent may be dead in 5 years. These latter figures coincide with Nesbit's (1945)[8] who states that of unoperated cases of renal tuberculosis, 81.3 per cent were dead in 3 years.

TABLE 1

AGES	CASES
0-10	0
10-20	10
20-30	26
30-40	43
40-50	23
50-60	10
60-70	5
Total	117

TABLE 2

FOLLOW UP PERIOD	PATIENTS TRACED DURING THIS PERIOD	PATIENTS LOST TO FOLLOW UP FOR THIS PERIOD	PATIENTS ALIVE		PATIENTS DEAD		CAUSE	
			No	%	No	%		
years								
0-3	96	0	89	92.5	7	7.5	Extrarenal tuberculosis Renal tuberculosis Peritonitis (non tuberculous)	4 2 1
3-5	77	12	72	93.5	5	6.5	Renal and pulmonary tuberculosis	5
5-10	62	10	55	89	7	11	Adrenal tuberculosis Renal tuberculosis Cause ?	1 5 1
10-15	39	16	35	90	4	10	Renal tuberculosis	4
15 plus	15	20	12	80	3	20	Hypertension Coronary occlusion Cause ?	1 1 1

Summarizing the reported statistics, it may be stated that about 50 per cent of patients have survived for 5 years after nephrectomy for unilateral renal tuberculosis.

The present study concerns itself with 117 patients with renal tuberculosis admitted to the ward service of the Mount Sinai Hospital from 1928 through 1945. Of these 117 patients, 106 were nephrectomized for unilateral renal tuberculosis, and 11 were not treated surgically either because of presence of demonstrable bilateral renal tuberculosis, or active extrarenal infection. Twenty-nine of the patients had complete ureteronephrectomy performed according to the technique of Beer,[9] and in the others, simple nephrectomy with removal of as much ureter as possible was done. The indications for ureteronephrectomy were tuberculous ureteral involvement with stenosis and dilatation. Of the 106 surgically treated cases, 2 died postoperatively and 8 were immediately lost to follow-up, leaving 96 cases that have been followed. Of the 117 cases, 71 occurred in males, and 46 in females. The age variations are presented in table 1. There were concomitant active pulmonary lesions in 15 cases, and genital or bone lesions in 15 cases preoperatively.

The results will be presented in tabular form (table 2). Following the method of Emmett and Kibler, the percentage of survival will be presented in relation to the number of cases not lost in follow-up clinic. Subsequently, 15 of the operative cases developed genital or osseous tuberculosis, and 17 cases developed contralateral renal involvement. There were also 17 cases of residual tuberculous cystitis. The average length of survival of the patients who developed genital or osseous tuberculosis postoperatively was 7.3 years; of those who developed contralateral involvement, 6.2 years, and of those who had residual tuberculous cystitis, 8.6 years.

During this period there were 11 instances of adnexal tuberculosis in the male in which no upper urinary tract lesions could be demonstrated. The age variation was between 24 and 79 years. The lesion in the 10 cases was unilateral epididymitis, and in 1 case bilateral epididymo-orchitis. Four patients had epididymectomy performed, 6 had epididymo-orchidectomy done and 1 was not operated upon. In all the operative cases, the diagnosis was confirmed by the pathological laboratory. The length of survival (and/or follow-up) varied from 1–15 years with an average of 6.4 years. In no case was there a development of gross upper urinary tract tuberculosis. One patient subsequently had a nephrectomy for a non-tuberculous calculous pyonephrosis. Two cases had associated pulmonary tuberculosis. Of these, one survived 4 years, dying of pulmonary tuberculosis, and one patient is living 15 years after epididymo-orchidectomy, with an arrested pulmonary lesion.

As indicated by the statistics of survival (table 2), nephrectomy for unilateral renal tuberculosis affords the patient a better than even chance for a 5–10 year survival. Even including the number of cases lost to follow-up, the survival rate for a 5–10 year period is 55 patients alive of 96 or 57.3 per cent. This figure is similar to the 60 per cent complete cures reported by Braasch[10] in 1921. An appreciable number of patients have survived more than 15 years and are ostensibly cured. For the present time, nephrectomy for unilateral renal tuberculosis has proven to be a time-tested and efficacious method of treatment. Until a long-followed series of cases treated solely with streptomycin can be shown to compare favorably with surgically treated cases, nephrectomy for unilateral renal tuberculosis, perforce, must be regarded as a reliable method of treatment.

17 E. 96 St., New York, N. Y.

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[9] Beer, E.: J. A. M. A., **77**: 1176, 1921.

[10] Braasch, W. F.: Am. J. Med. Sc., **159**: 8, 1920.

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THE CLINICAL MANAGEMENT OF CYSTIN LITHIASIS[1]

LINWOOD D KEYSER AND CHARLES D SMITH (BY INVITATION)

While cystin lithiasis is a comparatively rare disease and the clinical experience of the individual urologist will comprehend only a few cases, its significance to the afflicted patient as well as its relation to the whole field of calculous disease prompts another review of the subject

Wollaston in 1810 described two unusual stones found in the urinary bladder as "cystic oxide" stones, the term "cystic" remarkably enough referring to the bladder Berzelius in 1833 suggested that such stones were composed of cystin In 1824 Stromeyer and Piont described the hexagonal crystals found in the urine, upon which the diagnosis of cystinuria is even now most frequently based Piont made the earliest analysis of cystin but believed it contained oxygen instead of sulfur Baudremont and Malaguti found that cystin contained sulfur and Thaulou finally analyzed the compound Later the structural formula of cystin was determined by Goldman and Bauman and Ehrlenmeyer

Cystin or di(B-thiol-a amino propionic) acid and its closely related cystein or B-thiol a amino propionic acid are the sulfur containing amino acids of the protein molecule Small amounts of cystin (0 8 to 84 mg daily) may be excreted in the normal urine The term cystinuria is applied to an inborn error of metabolism in which cystin is present in the urine in consistently abnormal amounts (0 4 to 1 gm daily) In cystinuria the neutral (protein) sulfur of the urine is increased while the inorganic sulfur is decreased It appears that in the normal metabolism cystin is in large part oxidized to sulfate, while a smaller and less significant amount is converted to taurin In cystinuria there is failure of oxidation of cystin to sulfate, the metabolism of the cystin conversion to taurin being undisturbed Cystin is related to methionine and to glutathione (a tripeptid of cystein, glutamic acid and glycine) Both methionine and glutathione can replace cystin in the dietary The reverse is not true (fig 1)

Feeding of cystin to cystinurics does not increase the excretion of cystin It is oxidized to sulfate Even cystin recovered from a patient's urine will be so oxidized when fed to this individual However, methionine and cystein feeding do augment cystin excretion Thus the cystin in the urine is probably derived from sulfur containing proteins and not from exogenous ingestion of cystin itself The cystin which is active in cystinuria is levorotatory while dextro-rotatory cystin does not replace the levorotatory variety in the metabolism

In short and without elaborating upon the biochemistry of the cystin metabolism much of which is confused, cystinuria involves some abnormality in the decomposition products of protein in which cystin is excreted as such and not oxidized to inorganic sulfate The cystin excreted when such an error exists is somewhat proportionate to the protein intake Reduction in the amount of protein reduces the excretion of cystin but does not eliminate it altogether In true cystinuria the substance will continue to be excreted even on a starvation diet. Again, alkalinization of the urine acts to dissolve cystin crystals but the alkalinization of the system also seems to influence the metabolism in such a way that excessive quantities of cystin are not formed and excreted as such.

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[1] Read at annual meeting, Mid Atlantic Section, American Urological Association, Hot Springs, Va , March 12, 1948

We may mention in passing that Yeh, Frankl, Dunn, Parker, Hughes and György have shown that there is a general disturbance of the metabolism of the amino acids in cystinuria. Fanconi described a syndrome in which cystinuria was related to stunted growth, rickets, hypophosphatemia, acidosis, glycosuria and high excretion of organic acids including amino acids. In Fanconi's syndrome cystinuria developes first, leading to renal injury followed by other metabolic changes characteristic of impairment of renal function (acidosis, hypophosphatemia, osteodystrophy). Cystin crystals may be found in organs and tissues and demonstrated in vivo by bone marrow biopsies.

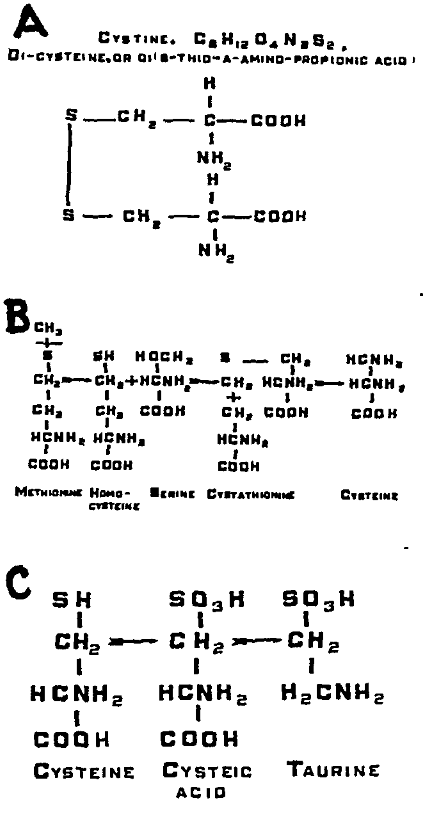

FIG. 1. *A*, structural formula of cystin. *B*, formulae, showing relation of cysteine to methionine. *C*, formula, showing relation of cysteine to taurine.

The condition of cystinuria is a permanent and life-long physiologic upset. In itself it may be and usually is innocuous, many cystinurics passing through life without knowledge of their metabolic abnormality. However, a certain probably rather small percentage of cystinurics are prone to form calculi in the urinary tract. This calculosis because of its marked tendency to recurrence is of an almost malignant variety.

A question immediately arises Why do certain cystinurics deposit calculi while the majority escape this complication? The answer is not easy and may involve the same processes that bring about calculosis in any type of excessive excretion of crystalline matter in the urine We note the relatively low incidence of calculi in hyperparathyroidism, in gout, in oxaluria and certain crystalline phosphaturias Experimental, pathologic and clinical evidence points to the probability that some lesion of the tubular epithelium of the kidney is a precursor of stone in these several conditions So it may be with the cystinuric To date no elaborate pathologic study of the kidney containing cystin stone has been made so we can only reason by analogy Cystin lithiasis must tentatively be considered an unusual type of hyperexcretory calculosis in which cystin deposition on damaged renal tubular epithelium takes place

INCIDENCE

Until recent years it was the occurrence of calculosis that called attention to the cystinuric clinically Frequently, but not always, the small colorless hexagonal crystals of cystin are found in the urine of such stone patients (fig 2) However, the failure to find cystin crystals with or without stone is not an adequate criterion for the absence of cystinuria By applying the qualitative cyanide nitroprusside test of Brand, Harris and Biloon and the quantitative estimation of the 24 hour output of cystin by the method of Sullivan and Hess, numerous cases of cystinuria without crystal or stone deposition have been found in routine urine examination Thus Lewis reports 29 positive Brand Sullivan tests in the routine examination of urines from 11000 healthy young men and women

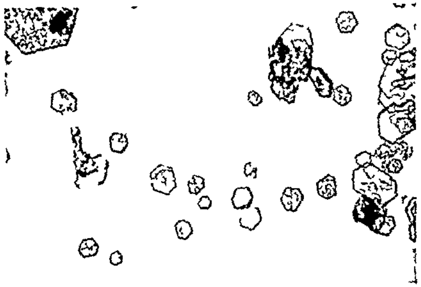

Fig 2 Cystin crystals

Simon encountered only one example of cystin crystalluria in routine examination of 15,000 urines while Primona found only one in 20,000 (Kretschmer)

Eppinger estimated that only 2 7 per cent of cystinurics develop calculi and Randall gives a similar percentage Segur and Kearns in 1925 found 124 cases of lithiasis in 181 cystinurics This work must be re-interpreted with regard to its significance as to occurrence of lithiasis in cystinuria, when we realize that many cystinurics without stone are never identified

As regards reported incidence of cystin stone, Link collected 112 cases in 1912. Kretschmer in 1916 collected 107 cases, later in 1933 adding 3 personal cases. Isolated case reports of one or more cases are infrequently reported but the total is not large.

As to the incidence in routine calculus analysis, Nakano found 7 instances of cystin calculi in a series of 600 cases (1.2 per cent) while Prien and Frondel found 3.8 per cent cystin stones in a series of about 700 calculi.

Males seem to be affected more frequently than females (about 65 to 27) (Kretschmer). There is no predilection in regard to age. The condition has been described in an infant of 12 months (Manly) and in a male of 80 years (Thompson). In general the disease appears in younger individuals. Whether or not cystinuria may be present at birth is not known.

Cystin calculosis is usually unilateral and when it recurs it usually does so at the same site. However, the disease may be bilateral and passage of small calculi, showers of crystals from one side or the other or the finding of cystin stones in the bladder are all noted in the literature. From a cursory review of the literature we find no estimate of the bilaterality of the condition. However, it is apparently infrequent and our cases number 2 and 4 are of interest in this respect.

FAMILIAL OCCURRENCE

A remarkable feature of cystinuria is its familial occurrence. According to Hawk the disease is transmitted as a Mendelian recessive. The hereditary tendency towards cystinuria has been established by numerous investigators among whom Thin and Robeson are noteworthy. Thus a cystinuric examination of the patient's family may reveal a considerable incidence of the disease in other members. Andrews and Brooks traced 24 descendants of an original cystinuric and found 6 positive cases of the disease. In one line of descent three successive generations were cystin positive while in the other line, four successive generations were alternately positive and negative. The original cystinuric (a girl aged 19 years) was the only member showing calculus formation. Kretschmer and others have given detailed reports of cystinuric families. Of 22 cases collected by Poland, 10 occurred in 4 families (Herman).

CLINICAL AND DIAGNOSTIC FEATURES

The clinical features of cystin calculosis do not differ greatly from stones of other composition in their immediate presentation. Frequently small stones or sand are passed and periodic ureteral colic may mark the picture. The stones in kidney, ureter, or bladder may be single or multiple. At times they may assume the contour of the calyx in which they form. However, massive stag-horn calculi are rare.

Infection is nearly always absent and when present is regarded as secondary in type from stasis or from metastatic infection from some other focus. The physical characteristics of cystin calculi are individual in type. Such stones are made up of small agglomerations of crystals with meager organic framework colored by a yellowish urinary pigment. Herman describes the cystin stone as loose in texture, soft, light, smooth or finely granular and yellowish On exposure to air they become yellowish-green or soap like The sectioned surface shows radiating striae Rarely lamination may be noted as in one of our cases Cystin calculi as a rule are composed of pure cystin with small amounts of organic matter but at times other elements are found Kretschmer reports a stone with a phosphate nucleus with surface deposition of cystin

Qualitative analysis of cystin calculus is determined in several ways When the stone is pulverized and the powder burned on platinum foil, a pale blue flame burns for a short time with a peculiar sharp odor The powder dissolves in ammonia and the characteristic six sided or hexagonal crystals are deposited as the ammonia evaporates

Again the powder if fused with sodium hydroxide (solid), and then acidified, gives rise to production of H_2S If the powder is treated with ammonia and sodium cyanide, it will give a deep red color on addition of sodium nitroprusside

Cystin stones are deposited in acid, neutral even slightly alkaline urine As will be further noted the amount of alkali needed to suppress cystinuria and to dissolve the crystals is variable with each individual As already mentioned, the finding of cystin crystals is also variable For this reason, the cyanide nitroprusside test should be applied to the urine of patients in whom cystin calculosis is suspected

The x-ray features of cystin stones likewise vary Herman states that pure cystin stones are invisible, lacking compactness Pure cystin placed in the stomach in capsules is invisible by x-ray With increased density large stones and those containing inorganic substances may be visible However, according to others, notably Holmes and Ruggles, cystin stones may be very dense and cast a shadow Beer states that large stones may cast a shadow while small ones may be non opaque Ewell feels that stones which do not cast a shadow are usually of cystin, xanthine or uric acid

RECURRENCE

The most ominous feature of cystin calculosis is its almost inevitable recurrence The history of almost all sufferers from this disease is one of repeated passage of stones, repeated periodic colics or the reformation of calculi after surgical removal Thus while cystin calculosis is rare, its management becomes a matter of grave concern to the individual patient who is so unfortunate as to suffer from this affliction

LOCALIZATION OF CALCULI IN THE RENAL PELVIS

At times cystin and other calculi which cast faint shadows in x-ray may be difficult to localize in the proper calyx of the kidney One of us (C D S), following a technique developed by J L Tabb of Richmond, Virginia, makes use of a blank 14 by 17 inch film This is accurately superimposed on the flat film or scout film The edges of the two films are fixed by metal paper fasteners The outline of any part of the kidney periphery when definitely seen is traced on the blank film with a wax pencil The outline of the stone shadow is likewise traced

The blank is then removed and placed over a pyelogram, retrograde or excretory (especially if this presents a good nephrogram). The outline of the kidney periphery is placed over that in the urogram and the stone shadow will be found localized at the proper site in the renal pelvis. This technique while only occasionally necessary has been found of value in localizing faint shadows which are not well seen in excretory urograms or entirely obliterated in retrograde pyelography. It has been helpful in our hands in localizing cystin stones (fig. 3).

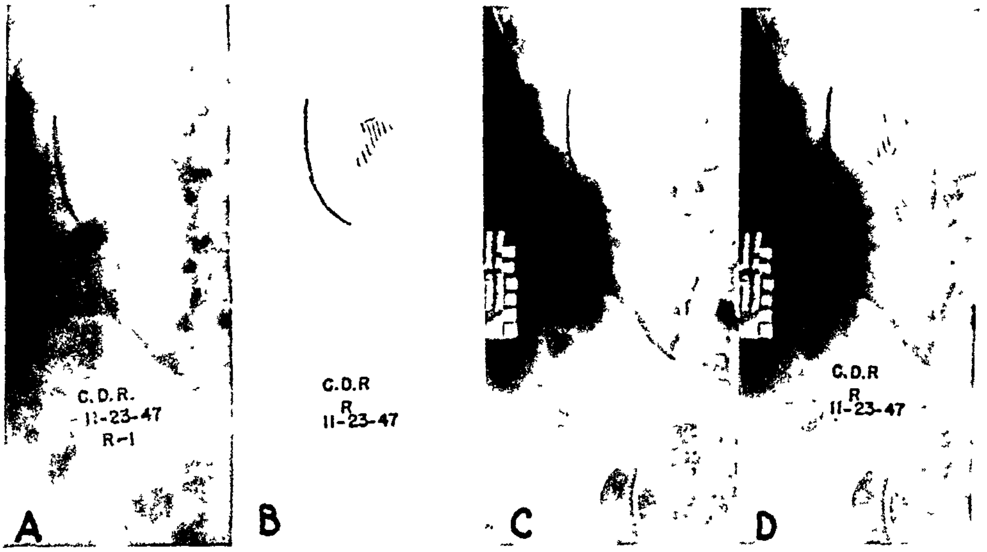

FIG. 3. Case 2. *A*, shadow of cystine calculus in right kidney region. *B*, blank film with part of visible periphery of kidney and outline of calculus traced thereon with black wax pencil. *C*, retrograde urogram. Faint shadow of stone is obscured. *D*, superimposition of blank film *B* on retrograde urogram *C* localizes stone in lower calyx. This technique of localizing stones accurately in renal pelvis has proved of value with cystin and other calculi which cast faint shadows in flat scout film.

TREATMENT OF CYSTIN LITHIASIS

Treatment must be planned in the light of probable recurrence. The fact that these patients have had or are likely to have multiple surgical or cystoscopic procedures must be a primary consideration.

As for efforts at dissolution, Crowell was able to dissolve a large stone in the right kidney and three small ones in the left of a 27 year old woman by urinary alkalinization and cystoscopic renal lavage every 2 to 3 days for 45 days and then weekly over a period of 9 months. The stones disappeared and likewise the crystalluria. Whether cystinuria persisted is not recorded.[2] This classical example of stone dissolution in cystin lithiasis (and so far as we know the first dissolution of any type on record) has not to our knowledge been repeated in a patient with larger calculi. We have attempted dissolution in one of our cystin cases and perhaps a few smaller calculi in one kidney were reduced sufficiently in size to pass through the ureter spontaneously. However, a larger cystin calculus in the opposite kidney did not diminish in size and perhaps became even larger after two years We have not applied the technique of retrograde continuous irrigation in cystin calculosis The one patient in whom it might have been attempted was not tolerant to indwelling catheters Nevertheless, this method of alkaline irrigation might be tried in selected cases and especially in early recurrences

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[2] Dr. Raymond Thompson, (Charlotte, N. C.) writes that this patient died of a heart attack 3 years after Dr. Crowell's report. At this time she had recurrent stone in one kidney.

If the patient has no visible x-ray shadows, and the ureters are unobstructed, but has a history of having had cystin calculi spontaneously passed or surgically removed, the regimen for prophylaxis against recurrence should be given We have not encountered a cystinuric without a history of lithiasis Such a patient would probably best be left alone until he does form stone or have colic from inspissated crystals

In treating calculosis in general we believe that as far as practicable effort should be made to free the urinary tract of all calculous material Especially is this true in cases where the stones have a metabolic error in their genesis and of course this is of the greatest moment in treating cystin lithiasis If we are able to start afresh with a urinary tract free of calculi, we will have a great advantage in preventing recurrence

The operations of pelviolithotomy, ureterotomy, cystotomy or endoscopic stone removal will not vary in technical detail in treating cystin calculosis from those used in other types of stone

HYDROSTATIC DILATATION OF URETER BELOW IMPACTED URETERAL CALCULUS

In 1 case of cystin stone impacted in the lower ureter, 4 cm above the ureterovesical meatus, we employed a technique of dilatation of the ureter below the stone with successful passage This procedure we believe warrants description The stone was invisible by x-ray but the patient had intense ureteral colic with pain in the left loin At cystoscopy the catheter met with impassable obstruction about 4 cm from the bladder Three 6 F catheters were passed up the ureter to this obstruction and the cystoscope carefully withdrawn leaving the catheters in situ for 20 hours They did not drain The distal lumina of two catheters were then plugged tightly with Victrola needles and into the third, 5 cc of sterile olive oil was injected under moderate pressure[3] The catheters were then removed and in a few hours the obstructing calculus was passed spontaneously The ureter around and just distal to the stone had been dilated sufficiently to permit the stone to become unimpacted and to pass We have used this technique in several instances with other types of stone To be successful of course, the stone must lie far enough up the ureter to permit the catheters to be held in situ

Stones of cystin may recur in the same calyx of the renal pelvis after surgical removal Dr Hugh Wyman of Columbia, South Carolina consulted one of us in 1946 concerning such a case in a young woman from whom he had previously removed a cystin stone from the lower calyx of the left kidney four times in about 12 years and who, at the time, had a recurrent calculus at the same site. We advised a partial nephrectomy, which was carried out. The lower pole of the left kidney containing the calyx and stone was removed in August 1946. Dr. Wyman writes us that the patient still shows crystalluria of cystin type but has had no recurrence of calculus since. She has been on a prophylactic alkaline ash diet and urinary alkalinization treatment since. We believe that calycectomy or removal of a stone forming calyx should be tried when possible if stones recur at a site which can be surgically extirpated.

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[3] The possibility of producing an oil embolus from such a procedure seems remote when we consider the frequent injection of oil medication intramuscularly or of radio opaque oils into sinuses for diagnosis without this hazard

PROPHYLAXIS AGAINST RECURRENCE

It is the general feeling that cystin stones will sooner or later recur and clinical experience with rare exception bears this out. If we are able to clear the urinary tract of cystin calculi, intensive effort at prophylaxis might either delay recurrence or hypothetically prevent it altogether. However, our personal experience with 4 cases which will be presented is inadequate to evaluate the principles we have employed.

We advise an alkaline ash diet low in sulfur proteins,[4] alkalization of the urine with drugs, removal of gross urinary obstruction and periodic atraumatic ureteral dilatation at 3 to 6 month intervals over a period of several years. This is a rather strenuous regime and has to be broken at intervals. We feel that an alkaline ash diet is more important than too rigid a limitation of the sulfur proteins. The alkaline ash diet itself has a few sulfur containing foods. Sodium bicarbonate in doses of 4 to 6 gm. daily, potassium citrate, or the effervescing drugs such as citrocarbonate, alkazane, etc., each have their place. The patient should be taught the use of indicator paper such as nitrazene or methyl red, and alkalinity should be maintained if possible at a level adequate to dissolve cystin crystals present in the urine.

As for the controversial subject of periodic ureteral dilatation as a prophylaxis against recurrent stone, it is difficult to prove or to disprove its scientific value. One of us has practiced this procedure over 20 years with all types of recurrent calculi and has been impressed with its merit. Cystoscopy is somewhat unpleasant but after a treatment or two with the patient hospitalized and under anesthesia, it can be repeated in the office as a rule without too much reaction. In dealing with cystin calculi we have used catheter bougies and irrigated the renal pelvis at each session with alkaline solution such as 1 per cent sodium bicarbonate or 1 per cent mercurochrome.

Under such a regime cystin crystalluria seems to clear up and probably cystinuria is diminished. Melvin and Andrews state that after operation the cystin excretion from the kidney operated on temporarily is diminished. However, it must be emphasized that the complete and permanent elimination of cystinuria seems an unlikely achievement at the present time. For this reason we advise check ups at intervals of three months in patients who have had cystin calculi, with x-rays and urograms at least twice yearly. This should be done, it would seem, over a period of years.

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[4] Foods high in sulfur content: beans, bran, bread, brussel sprouts, cabbage, cauliflower, cheese, clams, cocoa, eggs, fish, macaroni, meats (lean), nuts, oats onions, oysters, peas, swiss chard, turnips, watercress, wheat.

CASE REPORTS

Case 1. R. S., R. H. No. 65311, a truckdriver aet. 32 years, had passed several small stones from the right ureter over several years. He had had cystoscopic treatment elsewhere. One of the calculi brought by the patient was found to be composed of pure cystin. He was admitted to the Roanoke Hospital May 27, 1944 having had persistent right ureteral colic for 3 weeks. The temperature was 99.8, pulse 100, respiration 20, hemoglobin 84 per cent (Sahli), slight leukocytosis (11600 white blood cells per c.mm.). Intravenous urography showed no dye excreted on the right but there was an opaque, elongated density in the course of the lower right ureter which we felt was probably a calculus. Diodrast was excreted on the left but in poor concentration. Blood urea was 42 mg. per cent. The urine was acid, *p*H 5, specific gravity 1.016, albumin trace, sugar negative, occasional blood cell and no pus cells. Numerous hexagonal crystals of cystin were noted in the sediment.

Cystoscopy under spinal anesthesia (metycaine 120 mg.) was done June 3, 1944. A catheter met obstruction about 3 cm. from the bladder. Attempts to pass a Johnson basket and the McKay multiple thread dislodger failed. Three 6 F catheters were passed with difficulty beyond the obstruction. These were allowed to remain indwelling for 5 days. The pain and febrile reaction subsided. Apposition x-ray films and retrograde urograms (June 7, 1944) proved the presence of calculus. The catheters were then withdrawn about 6 cm. and the outlets of 2 catheters plugged with Victrola needles. Into the third, 5 cc of sterile olive oil was injected under moderate pressure after which all three catheters were withdrawn. The stone passed spontaneously after 18 hours. It was found to consist of pure cystin and was unusually hard and dense.

This patient was placed on an alkaline ash diet and given a citrate-bicarbonate "alkaline diuretic mixture", with instructions as to the use of indicator paper.

Several ureteral dilatations and alkaline lavage of both pelves were carried out at 3 month intervals. While on alkaline regime the crystals were absent from the urine but on resuming an acid diet they reappeared. This patient has had no recurrence of stone or colic for nearly four years. Yet, is he cured?

Case 2. C. D. R., R. H. No. 68599, an attorney aet. 23 years, was admitted to Roanoke Hospital August 24, 1945 with intense left ureteral colic. He gave a history of passing of small calculi at intervals of 3 to 9 months over 7 years. These had been found to consist of cystin. In November 1941 a cystin stone had been removed from the right renal pelvis elsewhere. He had been advised to keep the urine alkaline but the regimen had not been consistently followed. There was no history of stone or of cystinuria in his family. Following the pelviolithotomy in 1941 he had had frequent attacks of kidney colic all on the left side and had passed numerous small stones every 6 to 8 months.

Recent excretory urograms made elsewhere showed a faint but definite opacity in the right kidney which we later demonstrated by the blank film superimposition technique to be located in the lower calyx. There were several less dense shadows in the left renal area. The temperature, pulse, and respiration were normal. Blood urea was 22 mg. per cent, uric acid 5.5 mg. Serum calcium was 10 mg. per cent and phosphorus 4.4 mg. per cent. Acid phosphatase was 3 units and alkaline phosphatase 3.5 units (King Armstrong). The urine was acid, pH 5.5, specific gravity 1.010, albumin trace, sugar negative, sediment, 8–10 white blood cells per high power field and 2–4 red blood cells. Numerous cystin crystals were noted.

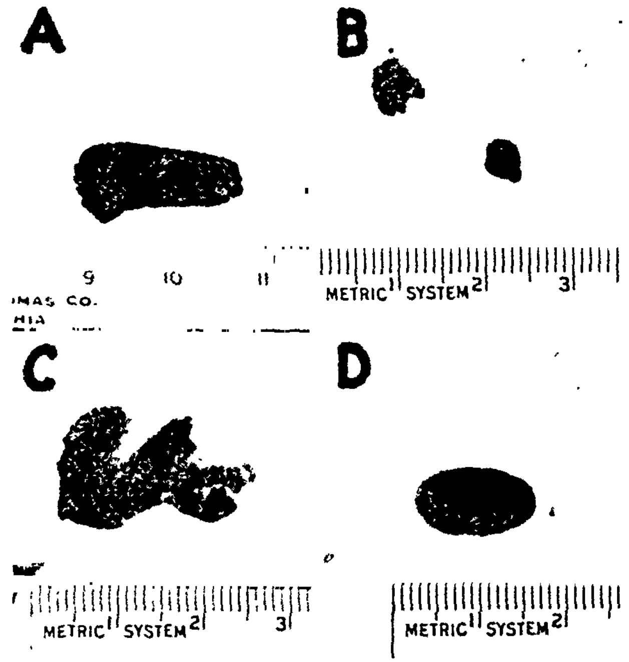

FIG. 4. *A*, case 2. Stone passed after hydrostatic dilatation of ureter below calculus. *B*, case 2. Two small stones passed from left ureter 2 weeks after ureteral dilatation. *C*, case 2. Stone removed from lower calyx of right kidney. This is calculus localized by film superimposition technique shown in figure 3, *D*, case 3. Laminated calculus of cystin and calcium phosphate removed by repeated cystoscopy and ureteral dilatation.

Cystoscopy on August 28, 1945 under spinal anesthesia (novocain 75 mg.), showed a definite fibrotic (collar contracture) bladder neck. The left ureter was catheterized and met with an impassable obstruction about 4 cm. from the meatus. Repeated efforts to pass this obstruction failed. We then dilated the ureter with a 12 F bougie to the site of obstruction and subsequently passed three 6 F catheters to the same point. The cystoscope was carefully removed and the catheters allowed to remain indwelling for 12 hours, when again we plugged the ends of 2 catheters and injected olive oil through the third under moderate pressure. The catheters were removed after 30 minutes and 8 hours later a stone consisting of pure cystin and measuring 1 by 1½ cm. was passed (fig. 4, *A*). During the next week two small calculi were passed with mocerate left ureteral colic (fig. 4, *B*). The patient was placed on a rigid alkaline ash diet and alkaline diuretics administered He has maintained his urine at an alkalinity of pH 7–8 since, with occasional breaks of a week during which the urine is acid Cystin crystalluria disappears when the urine is alkaline but the cyanide nitroprusside reaction for cystinuria persists X-rays after 1 month showed no opacities in the left renal area and the ureteral catheter could be passed to the left kidney without obstruction

The patient had periodic ureteral dilatation on both sides for 2 years However, urinary alkalization did not cause a decrease in size of the right renal calculus In fact, it seemed to gradually become more dense and perhaps larger In November 1947 a cystin stone was removed from the right lower calyx by pelviotomy (fig 4, *C*) Convalescence was marked by oliguria for several days and a rise in the blood urea to 79 mg per cent Diuresis and return of kidney function (never too good as his Diodrast excretion was always poor) ensued with a smooth convalescence

In January 1947 the patient had a 7 F catheter passed to the right renal pelvis and the kidney was lavaged with weak bicarbonate solution X-ray showed no stone shadows His alkaline regimen has been continued The left kidney and ureter have been free of stone for 31 months We are watching the further clinical course with guarded prognosis but with hope that the cycle of recurrence may be indefinitely inhibited

Case 3 C D H, R H No 66029, a railroad brakeman, aet 45 years, was admitted to Roanoke Hospital August 28, 1944 He gave a history of passing several stones from the left kidney during the past 3 years The present attack started 3 days before admission and colic requiring morphine had been persistent There was no history of stone in the family The temperature was 99 8 F, pulse 100, respiration 20, leukocytes 11200 The urine was acid, *p*H 5 5 specific gravity 1 017, albumin negative, sugar negative A few red and white blood cells and a few hexagonal colorless crystals (cystin) were noted in the sediment X-ray revealed an opacity 1 cm in diameter in the region of the left lower ureter Intravenous urography revealed normal renal pelvic delineation on the right but no dye appeared on the left side

Cystoscopy (August 29, 1944) A catheter passed up the left ureter met with obstruction 1 cm up This was passed with slight difficulty and three 6 F catheters were passed alongside After removal of these catheters the stone failed to pass and the patient had colic and febrile reaction September 2, 1944, a second effort was made and the stone was found in the intramural portion of the ureter Two 6 F catheters could be passed and were allowed to remain for drainage Pain and fever subsided In September a final effort was made to recover the stone by cystoscopy and ureteral dilatation and was successful The stone passed to the bladder and was recovered It was 1 5 cm in diameter and consisted, on chemical examination, of cystin with some phosphate (fig 4, *D*) It was laminated The patient was discharged and was seen at the office several months later He had not followed his alkalization program well and cystin crystals were still present X-ray was negative for stone shadows The patient was urged to follow the prophylactic regimen but has not been seen by us since Follow up letters have been returned, so we have not been able to observe the clinical course to date.

Case 4. J. K. M., R. H. No. 69892, a miller, aet. 56 years, was admitted to Roanoke Hospital February 28, 1946. He complained of intense right ureteral colic for 24 hours. X-rays showed no shadows at this time. With intravenous urography no dye appeared on the right while there was normal excretion on the left side.

Cystoscopy, February 28, 1946, under spinal anesthesia (novocain 50 mg.): The catheter met with dense obstruction on the right just above the bladder. Several catheters were finally passed and 25 cc of clear urine obtained. The catheters were removed after 24 hours. The patient was relieved of pain and was discharged. Four days later he reported that he passed a small stone but this was lost and unfortunately not analyzed. The patient had another right mild colic in August and the right ureter was dilated with a No. 10–11 Ashcraft *bougie. Following this a few particles of sand were passed.* No cystin crystals had been noted in the urine up to this time, but they may have been missed. March 7, 1948, the patient was admitted with left renal colic, nausea and vomiting. The urine showed a moderate number of cystin crystals and gave a strong cyanide-nitroprusside test for cystin. Cystoscopy was done on March 8, 1949, the left ureter being catheterized with three 5 F catheters. After their removal 24 hours later, a small cystin stone was passed with relief of pain.

N. B. Since presenting this paper this patient has been followed over a number of months with recurrent left renal colic. In the fall of 1948 a left pelviotomy was done for the removal of two cystin calculi which cast faint shadows in x-ray. A larger and at present asymptomatic stone has formed in the right renal pelvis. This will probably require surgical removal later. Periodic ureteral catheterization and urinary alkalization with diet and drugs are being carried out.

CONCLUSIONS

Cystinuria is an inborn error of metabolism occuring once in 11,000 to 20,000 patients. Cystin stone occurs in 3 to 4 per cent of cystinurics. These figures are approximate.

In cystinuria the oxidation of sulfur containing protein is upset so that cystin is not oxidized to inorganic sulfate. Cystin lithiasis probably arises from deposition of cystin crystals on a previously injured site of renal excretory epithelium. The disease is marked by persistent recurrence of calculi after they are passed or removed by surgical methods. A prophylactic regimen of urinary alkalization with alkalizing drugs and an alkaline ash diet is proposed. Periodic ureteral dilatation and lavage of the renal pelvis with weak alkalies are suggested. By these means we have some evidence that the recurrence time may be prolonged. Its permanent prevention is unlikely with present methods of treatment.

A technique of localization of faint shadows in the renal pelvis is described and a method of dilating the ureter below calculi impacted several centimeters above the bladder to allow disimpaction and passage of the stone is presented.

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NEUROGENIC DISEASE OF THE BLADDER: THE SURGICAL MANAGEMENT OF ITS COMPLICATIONS[1]

JAMES H. SEMANS

The incidence of neurogenic disease of the bladder and its surgical complications has risen with the increasing survival of patients with lesions of the spinal cord. Surgical treatment is important in their clinical management.

The two purposes of this report are to evaluate the new procedures and to mention those modifications of accepted techniques which have proved important in neurogenic vesical disease.

Description of the dysfunction present is still confused by varied terminology. Definition of terms is, therefore, indicated.

Neurogenic and neurological bladder are synonymous clinical entities. They denote abnormal function resulting from disease or injury of the vesical nerve supply. The term cord bladder is reserved for dysfunction secondary to lesions confined to the spinal cord.

Urinary retention is a common result of damage to the vesical nerve supply. The musculature of the bladder wall, the detrusor, contracts too feebly to expel urine through the urethra. At rest, however, it is hypertonic; that is, it fails to relax normally when the bladder is almost empty, and during filling. This is demonstrated during cystometry by recording the intravesical pressure.

Overflow incontinence occurs if retention is not relieved. This is believed to be secondary to injury of the nerve supply of the external sphincter mechanism.

The contracted spastic bladder is a less common result of neurogenic disease or injury. Only a few cubic centimeters of urine can be retained. The intravesical pressure is high. After less than 100 cc have been added during cystometry, fluid either leaks around the catheter or flows over the top of the water manometer.

ETIOLOGY

Langworthy has mentioned neurogenic disease of the bladder as a complication of cerebral vascular accident, brain tumor, parkinsonism, epilepsy, encephalitis, asymptomatic neurosyphilis, syringomyelia, Friedreich's ataxia, myotonia atrophica, acute anterior poliomyelitis, transverse myelitis, meningomyelitis, disseminated sclerosis, tabes dorsalis, syphilitic paraplegia, amyotrophic lateral sclerosis, subacute combined sclerosis, spina bifida, psychosomatic dysfunction, or tumor or injury of the spinal cord. Neurogenic urinary retention may also follow such surgical procedures as chordotomy and radical resection of the rectum. The vesical nerve supply is exposed to mechanical injury during both procedures.

DIAGNOSIS

The diagnosis is made by means of the history of neurological disease or injury, abnormal neurological findings, cystometry, inability of the patient to void without leakage and palpation of the distended bladder.

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[1] The content of this paper is based, in part, on the author's experience while chief of the Urologic Surgery Section, McGuire General Hospital, Neurosurgical Center, Richmond, Va. from 1944 to 1946.

SURGICAL TREATMENT

The common indications for urological surgery in neurogenic disease of the bladder are 1) to relieve urinary retention, 2) eliminate incontinence, 3) remove calcific concretions, 4) establish drainage of associated infections, 5) or repair chronic defects such as diverticula and fistulas. The ultimate aim of these procedures is the voiding of minimally infected urine without leakage or retention.

Spontaneous return of function of both the detrusor and sphincter often occurs. Therefore, accurate prognosis of the disease or injury is indicated before surgery is advised.

Lesions of the spinal cord. It is essential to determine when possible not only the site and extent of damage to the cord, but also whether this damage is temporary or permanent.

The site and extent of the damage will foretell, in part, the type of vesical function to be expected. Figure 1 illustrates this relationship. It is assumed in this diagram that, at any one level, all tracts of the cord are involved.

In the majority of the cases, however, the lesion is only partial; that is, not all fibers are destroyed. Intact fibers may not function for several months. This delay has been ascribed to the gradual disappearance of local hemorrhage or edema.

Emmett in 1948 reported difficulty in correlating the type of vesical dysfunction with the site, severity or completeness of the lesion in the spinal cord.

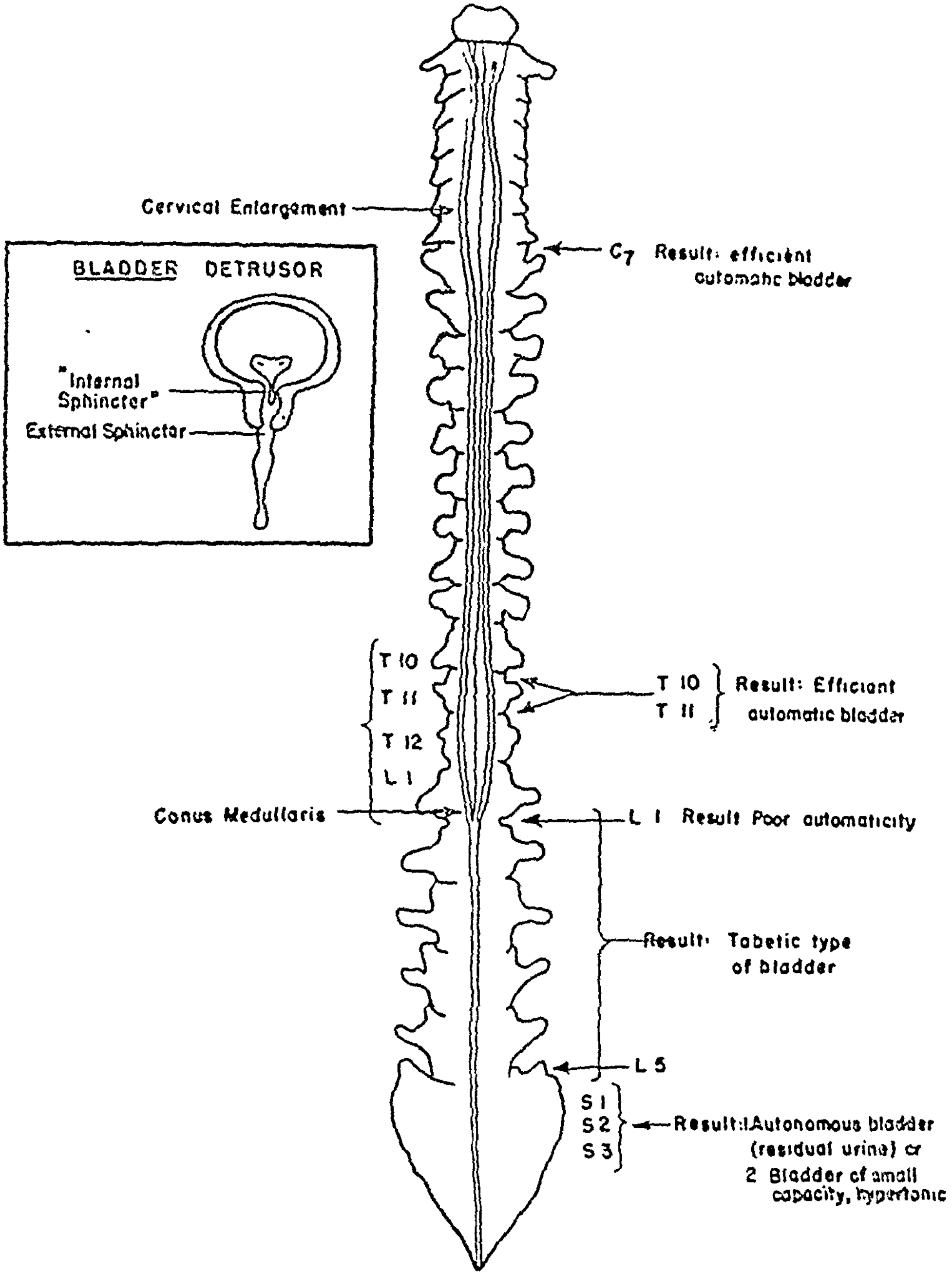
The reflex pathways between the bladder and spinal cord lie below the thoracic level. Therefore, even complete destruction of the cervical or thoracic portions of the cord should interrupt only the cerebral control of voiding. An automatic bladder should be the ultimate result. As the bladder distends, either stretching of the detrusor or cutaneous stimulation of the suprapubic, genital, or anal regions may initiate voiding. No cerebral control is necessary. This is termed automatic or reflex voiding. Emptying is frequently incomplete.

Any injury or disease below the level of the twelfth thoracic dermatome may involve the reflex neural pathway between the detrusor and spinal cord. Therefore, the bladder cannot be expected with certainty to empty itself well by reflex contraction of the detrusor.

Severe injuries below the twelfth dermatome may destroy the arc completely. The result is equivalent to a bladder without nerve supply. The muscular fibers of the detrusor contract without integration and do not empty the bladder. This is spoken of as an autonomous bladder. The amount of residual urine is large. Overflow incontinence occurs. Occasionally, a lesion at this site will result in a bladder of very small capacity with constant urethral leakage.

The permanence of the traumatic lesions is more uncertain than might at first be expected. In partial lesions, for example, it is difficult to determine always, even by exploration of the cord, whether all neural tracts are destroyed and what permanent loss will occur. However, 1) laminectomy, 2) x-ray evidence of marked vertebral over-riding (fig. 2) or 3) failure after a year to demonstrate return of function usually gives satisfactory evidence of the permanence of a lesion.

Suprapubic cystostomy. This procedure is indicated when drainage of the bladder by urethral catheter is impractical. Lack of facilities for close observation and nursing care is the commonest reason for its use. Other indications are incontinence in the female, periurethritis, periurethral abscess and epididymitis, when these infections remain unaffected by chemotherapy or antibiotics.


Cervical Enlargement
BLADDER DETRUSOR
"Internal Sphincter"
External Sphincter
C7 Result: efficient automatic bladder
T 10
T 11
T 12
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T 10
T 11
Result: Efficient automatic bladder
Conus Medullaris
L 1 Result Poor automaticity
Result: Tabetic type of bladder
L 5
S 1
S 2
S 3
Result: 1 Autonomous bladder (residual urine) or
2 Bladder of small capacity, hypertonic

Fig. 1. Diagram, showing correlation of level of injury and abnormal types of micturition, if damage is complete at stated level. Emmett finds this correlation difficult.

However, cystostomy can often be avoided by using urethral catheter drainage until retention disappears spontaneously.

The surgical technique has been described by Boyd.

Prather in 1944 urged that the cystostomy tube be left in the bladder at a level which prevents its impingement on the urinary trigone. He also recommends that the tube be brought through the upper end of the bladder in an oblique course to the skin. Healing is then more rapid, once the tube is removed. This high location of the tube enables the operator to reopen the bladder safely, if it becomes necessary. There is a wide space for dissection between the sinus tract and the symphysis. The tract protects the peritoneum from surgical injury.

If the patient has had generalized spastic seizures, 2 stay sutures of silkworm gut, which include muscle, fascia and skin, should be left in place for 2 weeks. These prevent dehiscence or herniation of the wound.

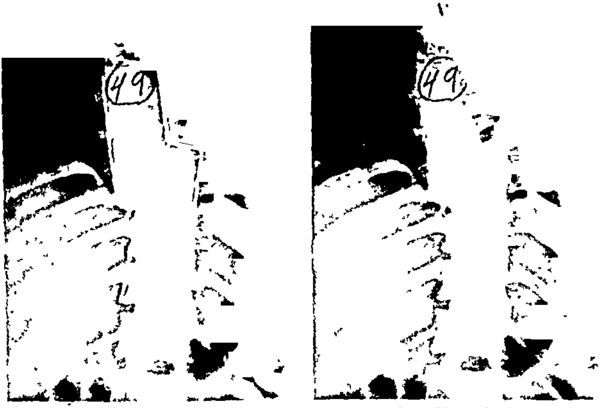
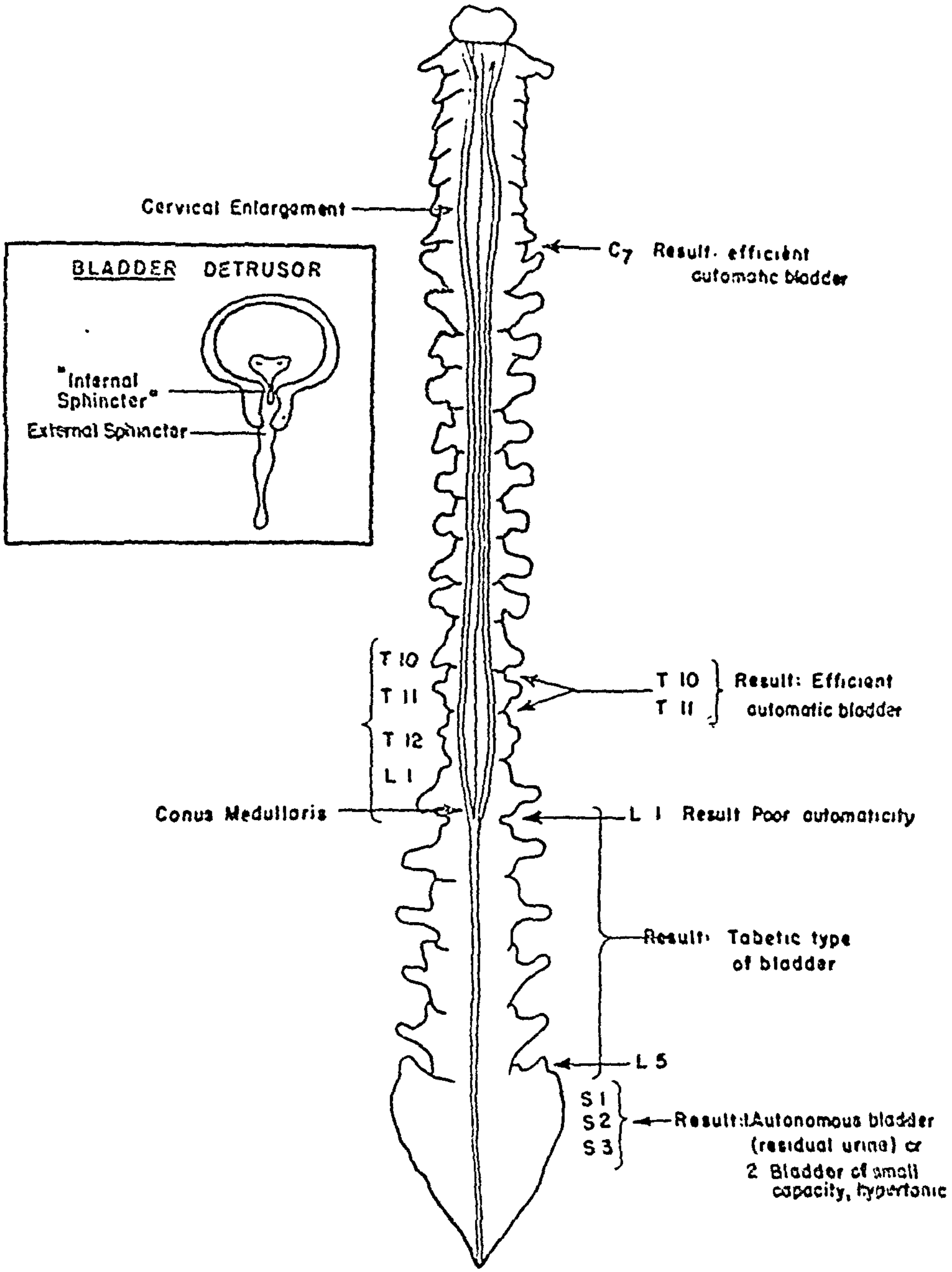


FIG. 2. Complete and permanent paraplegia at level of T-10 Marked overriding. All tracts permanently functionless at this level.

The catheter is changed weekly, beginning 2 weeks following cystostomy. Later the bladder capacity is maintained at 300 or 400 cc by daily stretching. Irrigations should be performed at least twice daily in the full prone position for maximum elimination of exudate from the base of the bladder (fig. 3).

Voiding test. This should be performed once weekly during the first few months, to detect the earliest signs of return of function. The bladder is filled through the suprapubic catheter and the catheter occluded. The patient attempts to void by straining, or by stimulating any area of skin which will incite reflex contraction of the bladder. After voiding is completed, residual urine is collected from the bladder through the suprapubic catheter and measured. When this is less than 90 cc, and the bladder capacity more than 250 cc, a urethral catheter can be inserted and the cystostomy allowed to close. If larger amounts persist, transurethral resection should be tried.

Surgical closure of suprapubic cystostomy. Too short a suprapubic sinus tract or abdominal spastic seizures may inhibit spontaneous closure of the cystostomy, der by urethral catheter is impractical. Lack of facilities for close observation and nursing care is the commonest reason for its use. Other indications are in-


Cervical Enlargement
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continence in the female, periurethritis, periurethral abscess and epididymitis, when these infections remain unaffected by chemotherapy or antibiotics.

However, cystostomy can often be avoided by using urethral catheter drainage until retention disappears spontaneously.

If anesthesia is necessary, 2 per cent procaine is injected superficially into the granulation tissue of the sinus wall and 30 cc of the same solution is instilled in the bladder. After 12 minutes, the suprapubic catheter is removed, the panendoscope inserted and the stone identified.

The bladder is then washed free of exudate. The grasping forceps are next inserted and the calculi crushed under direct vision. Care must be taken to avoid injury of the mucosa with the jaws of the forceps. The calcareous debris is removed by irrigation through the panendoscope. The remaining fragments are extracted instrumentally. They should be small enough to pass through the sinus tract without severe abrasion of the granulation tissue. It is often necessary to use the McCarthy panendoscope (24 F) intermittently for irrigation to insure good visualization.

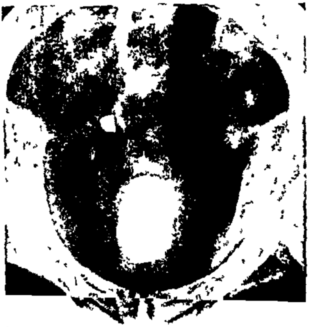

FIG. 4. X-ray of pelvis, showing vesical calculus in paraplegic patient. Calculus removed by transurethral litholapaxy. (Dimensions, after correction for roentgen magnification, 4.1 cm. by 2.8 cm.)

The suprapubic catheter is re-inserted. After turning the patient completely onto his abdomen (fig. 3), the catheter is again irrigated. Small particles lying in the region of the trigone are thus removed. The bladder should be inspected monthly until stones are consistently absent.

Transurethral litholapaxy. Large friable stones are removable by instrumentation through the urethra (fig. 4). The technique is identical with that used in suprapubic litholapaxy.

Many urologists prefer the Bigelow lithotrite. However, this attitude is changing with the improvement of visual lithotriptoscopes.

Avoidance of bleeding allows longer intervals between irrigations for crushing the stone under vision. The sheath of the panendoscope has then to be inserted less frequently for removal of clotted blood. Blood transfusion is given before signs of shock appear. Any early sign of shock is an indication for delaying further instrumentation until a second sitting or until shock has disappeared.

Transurethral resection. If the patient is unable to void after 6 months, it is indicated to reduce the urethral resistance to the weakened detrusor. This can frequently be accomplished by transurethral resection of the vesical neck and prostate, even though the former may be widely patent (fig. 5).

In the absence of prostatic hyperplasia, the amount of resected tissue will not be great. In 1940 Emmett pointed out that it is not sufficient to remove only 1 or 2 pieces of tissue from the posterior vesical lip. The entire circumference of the vesical neck and as much prostatic tissue as possible should be resected. Between 1 and 5 gm. is the usual total weight of the specimen.

To accomplish this, the following technique has proved helpful. Under vision, the cutting loop of the McCarthy electrotome is placed slightly on the vesical side of the bladder neck with the right ureteral orifice in view at 7 o'clock. By moving the working element, the instrument can be withdrawn to the verumontanum without moving the loop. Using the cutting current, the loop is then drawn only through the mucosa of the vesical neck. The first cut must be shallow in order to avoid perforating the bladder. The original groove is made deeper by removing more tissue until the transverse muscular strands of the vesical neck have been cut to a depth of 1 or 2 mm. Similar cuts are made on the left side at 5 o'clock. The intervening tissue, as well as the remaining circumference of the vesical neck, is now resected as deeply as the grooves at the site of the original 2 cuts. Prostatic tissue between the vesical neck and apex of the prostate is removed until the fibers of the capsule are seen.

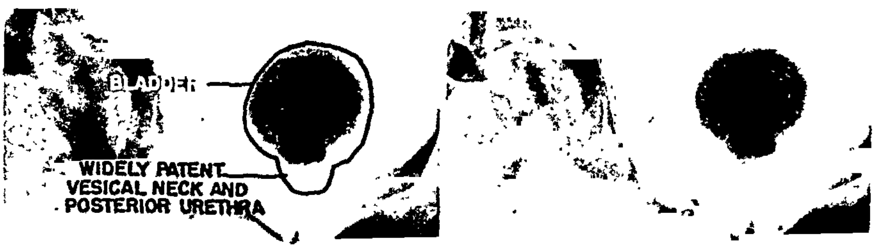

FIG. 5. Cystogram in patient completely and permanently paraplegic at level of T-7—T-8.

Spurting blood is controlled by fulgurating the arteries and veins. Dark, oozing venous blood from this area is best controlled by traction on a hemostatic catheter. Persistent fulguration of these venous sinuses may result in perforation of the prostatic capsule. Thrombin (20 units) may also be used at intervals after operation. The material is injected through the catheter with the bladder empty and the balloon deflated. The catheter is occluded for 30 minutes. Frequent irrigation of the bladder, as practiced in the past, has proven unnecessary. Insertion of a panendoscope, evacuation of blood clots and fulguration of only the actively bleeding vessels is more effective.

Perforation of the non-hypertrophied vesical neck and prostate may occur. Any question of this should be settled before the patient leaves the cystoscopic table. A cystogram is made after injecting 120 cc of 5 per cent diodrast, neo-iopax or skiodan into the catheter with the hemostatic balloon deflated.

If voiding does not recur after 3 months, resection is repeated. Minimally obstructing tissue should be removed.

Results: This operation has undoubted value in relieving retention of urine in many cases of paraplegia. Prather and Petroff in 1947 reported the early experience of urologists in Army hospitals. Of 33 cases of paraplegia there were satisfactory results in 19 and failures in 14.

In another series of 58 cases reported by Thompson, Nourse and Bumpus, Jr., in only 1 was the patient unable to void following repeated transurethral resection. In 5 cases, 3 transurethral resections were required. Results were considered satisfactory if there was not more than 2 ounces of residual urine.

Perineal urethrostomy. Lewis has described the advantages of perineal urethrostomy for drainage of the bladder by catheter. This procedure provides dependent drainage, in contrast to suprapubic cystostomy. The risk of periurethral abscess is much less than with a catheter in the anterior urethra. Prostatitis and epididymitis are contraindications, and may follow the procedure.

In some cases surgical closure of the tract has been necessary. To avoid this, at the time of urethrostomy, the skin is closed posteriorly, below the point of entrance of the catheter. A long tract is thus effected. This may hasten healing when catheter drainage is no longer necessary.

Membranous urethrolysis and urethroplasty. These are 2 surgical procedures used in 17 cases by the author to relieve urinary retention following injury of the spinal cord. Because of postoperative incontinence in some of the cases, these operations are not advocated unless the other procedures have been unsuccessful in relieving retention of urine. It is essential that as much tissue as possible be already removed from the vesical neck and prostate by transurethral resection.

Membranous urethrolysis (1 case) is believed to be effective because of disturbance of the nerve supply to the membranous urethra. The operative technique for exposure of this structure is identical with that described by Young in his radical perineal prostatectomy.

A sound is inserted to identify the membranous urethra. A gooseneck clamp is passed around the urethra midway between the prostate and urogenital diaphragm. The jaws of the clamp are opened widely, freeing the urethra from the periurethral tissues, without opening into it. A Penrose drain is inserted for 48 hours. Six vertical mattress sutures of black silk close the incision in the skin. The drain is sutured to the skin on the right side. An indwelling urethral catheter is not necessary.

Membranous urethroplasty is also identical with the technique of Young's perineal prostatectomy in regard to exposure of the membranous urethra. After the gooseneck clamp has been passed behind the urethra, the sound is removed and the urethra transected near the apex of the prostate. The procedure described by Vest for anastomosing the membranous urethra is applied here. Four mattress sutures of plain catgut are passed through the prostate at its apex. Each of the 8 long ends is rethreaded onto a large curved needle and guided first through the lumen of the external sphincter, and then through the wall of the bulbous urethra and subcutaneous fat of the anterior portion of the perineal incision. A splinting urethral catheter is passed through the entire length of the urethra into the bladder. Ligation of the sutures in the subcutaneous tissue of the perineal wound reapproximates the prostate and urogenital diaphragm around the catheter. The wound is closed, as in membranous urethrolysis.

Postoperative urethroscopic measurements show that the membranous urethra is shortened. Urethrometry demonstrates that the urethral resistance is reduced approximately 20 per cent.

Stricture was a complication in 1 case. Postoperative bleeding is controlled by using traction on a hemostatic catheter with the balloon inflated for as long as 12 hours, if necessary.

The lowering of urethral resistance in these cases suggests that maintenance of urinary retention after repeated transurethral resection may be caused by the external urethral sphincter, as suggested by Emmett in 1948. However, in 1 case with complete paraplegia below T-10 only that portion of the external sphincter mechanism lying between the urogenital diaphragm and the apex of the prostate was contracted. The portion of the external sphincter within the urogenital diaphragm had a semilunar shape. It was apparently incompetent.

Unilateral and bilateral pudendal neurectomy. The operation in man has been reported by Huggins in 1939 and 1948 by Emmett. The technique has been described by Huggins.

The purpose of the procedure is to reduce the resistance of the external urinary sphincter by severance of its peripheral nerve supply. The weak detrusor should then be able to expel urine from the bladder more completely.

Results: Of 6 cases treated by unilateral neurectomy, Huggins reported moderate improvement in 5 during a period of a year or less. In 4 cases not incontinent before operation, no postoperative urinary or fecal leakage occurred. In 1 case bilateral pudendal neurectomy was done. There was urinary stress incontinence, but no fecal incontinence. The residual urine decreased only after transurethral resection of the prostate. The late results in these cases have not justified extensive use of the procedure. (Personal communication 8 years later.)

Nesbit reports by personal communication a case with more favorable results. The patient had an extradural abscess involving the cauda equina, with neurological signs of complete destruction of nerves supplying the perineum on one side. There was a large amount of residual urine. Transurethral resection was not considered, since no obstruction could be seen. On the uninjured side the branches of the pudendal nerve supplying the membranous urethra were sectioned. This procedure did not impair sexual function. The patient was able to empty his bladder without incontinence when he was last seen, 2 years after operation.

Presacral neurectomy. The rationale of this procedure is based upon the hypothesis of an antagonistic action between the sympathetic (bladder filling) and parasympathetic (bladder emptying) innervation of the lower urinary tract. In injuries involving the sacral segments of the cord, the parasympathetic fibers leading to the bladder are frequently damaged. On the assumption that an antagonism exists, an imbalance of muscle tone, in favor of the undamaged sympathetic innervation, would account for the urinary retention. Surgical resection of the hypogastric plexus (presacral nerve) might be expected to correct this imbalance.

Pearl and Strauss have reported the details of technique. They stress the importance of supplementing the operation with sacral ganglionectomy.

Anatomy: Weinstein has described the varied anatomy of the hypogastric plexus. A single presacral nerve was found in only 4 per cent of his dissections. At least 2 presacral nerves, or a plexus, were found in the others.

Results: Learmonth reported postoperative reduction or elimination of residual urine associated with inflammatory disease of the spinal cord. However, in 1939, Huggins and others reported transient benefit only. The procedure is still used with success in dysmenorrhea and intractable pain of vesical spasm (Pieri).

It must be remembered that presacral neurectomy removes the nerve supply of the seminal vesicles. Since these organs are no longer able to contract after operation, no seminal fluid is emitted during coitus. The patient should be forewarned of this functional sterility.

Bilateral section of the third sacral nerve. Hoen in 1945 described this operation for relief of chronic urinary retention following injury involving the sacral segments of the spinal cord. The intent of the procedure was to lessen the tone of the external urinary sphincter by reducing its nerve supply.

The region of the third sacral nerve was infiltrated with novocain bilaterally in 2 cases in which retention of urine was the only evidence of residual neural damage. There was temporary relief of urinary retention. On this basis both third sacral motor roots were sectioned.

Operation: A small midline incision was made over the first sacral segment. The cul-de-sac of the dural tube was exposed by trephine and the dura opened. The third sacral root on each side was identified by counting caudad from the first sacral foramen. The motor component of each third sacral root was sectioned. The incision was closed in layers without drainage.

Results: After operation, voiding was satisfactory for 1 year. Urinary leakage then occurred.

Emmett in 1948 reported a case of a 30 year old man with persistent retention of urine. Transurethral resections on 3 occasions and sections of both pudendal nerves had been unsuccessful. The cauda equina was then ligated above both anterior and posterior roots of the fourth and fifth lumbar and all sacral nerves. After 6½ months the residual urine was less than 60 cc. He remained dry if less than 250 cc was allowed to accumulate in the bladder.

Tidal drainage. This method of automatically irrigating the bladder was first used by Laver and has been improved and popularized by Munro. It has been advocated by the latter to replace surgical procedures for relief of urinary retention.

The importance of tidal drainage in the care of the bladder in spinal cord injuries was summarized thus by Prather in 1947: "It is an excellent method to care for drainage and irrigation of the bladder . . . it is not necessary for rehabilitation of the bladder to a voiding state."

Intermittent irrigation. A practical method is that of intermittent irrigation (fig. 3). This is a satisfactory method of maintaining adequate bladder capacity and of keeping the bladder clean.

Incontinence. The intermittent incontinence of automatic voidings can be managed by emptying the bladder at regular intervals. The surgical treatment of neurogenic incontinence, especially in the male, has not been highly successful. Permanent diversion of urine by suprapubic cystostomy, perineal urethrostomy, a Cunningham penile clamp, or an incontinence bag has been necessary.

Recently, Foley has devised an "artificial sphincter." This is an inflatable ring which compresses the corpus spongiosum of the pendulous urethra, except during micturition. The ring is interposed surgically between the corpus spongiosum and corpora cavernosa. It has also been used around the entire circumference of the penis.

Emmett in 1948 reported benefit in 2 female patients treated by transurethral resection of the vesical neck combined with a Kelly plicating stitch in the region of the external sphincter.

Hoen in a personal communication described treatment of neurogenic incontinence by transplanting the eleventh intercostal nerve intradurally and anastomosing it to the third sacral nerve. Continence returned after 4 months. Insufficient time has elapsed for final evaluation.

The detailed technique of common urological surgical procedures has been well described by Dodson. However, in the patient with paraplegia, description of special aspects of certain of these is indicated.

Meatotomy is employed if there is not ample space for the escape of urethral exudate around an indwelling catheter. This can usually be determined when the catheter is first inserted. The operation is minor in comparison with the sequence of periurethritis, abscess and diverticulum or fistula, which may result from failure of the exudate to drain. The procedure should be used as prophylaxis and not postponed as therapy.

Antibiotics may not be effective in resolving periurethral inflammation or abscess. Intraurethral drainage should then be tried by using moist heat and digital pressure against the abscess. If the abscess opens intraurethrally, it should be emptied each day by pressure. By this simple procedure, the formation of diverticulum or urinary fistula may often be prevented.

Incision and drainage of a periurethral abscess through the skin may be necessary. This frequently results in a urinary fistula, which may close spontaneously or require plastic repair later. If the urethral fistula does not close within a few weeks, the indwelling catheter should be removed, even if cystotomy or perineal urethrostomy is required. Surgical closure is delayed until edema around the tract has disappeared. Six months may be necessary.

Repair of rupture of the urethra and bladder. Instrumental injury of the anesthetic urethra or bladder has occurred. The diagnosis in the paraplegic patient must be made by the operator, since there is no early symptomatology. Extravasation can be demonstrated immediately by x-ray after filling the bladder or urethra with radiopaque fluid. Any medium suitable for intravenous pyelography, used as a 20 per cent solution, will be non-irritating for this purpose.

Immediate surgical repair and suprapubic cystostomy are indicated as soon as shock has been controlled The surgical drainage tract must extend to the site of rupture A stab wound in the lower abdominal quadrant may be used

The mortality, reported by Culp in 33 cases, was nil if drainage was effected within 2 hours after the accident, and 100 per cent if postponed from 2 to 4 days If the patient survived 5 days, the mortality was 66 7 per cent

Removal of renal and ureteral calculi Calculi in the upper urinary tract are managed conservatively Surgical removal of stones is postponed, if possible, until the patient can remain ambulatory after operation Recumbency is conducive to recurrence of the calculi Nephrectomy is avoided because of the likelihood of urolithiasis in the remaining kidney, if this is not already true at the time of operation

In surgery of the ureter and kidney in the paraplegic patient with mass reflexes, stay sutures are mandatory Dehiscence has occurred, when this precaution has not been taken

SUMMARY

Numerous surgical procedures devised for neurogenic disease of the urinary bladder and its complications are described and evaluated

Suprapubic cystostomy is indicated for management of vesical retention when continuous and intermittent urethral drainage is impractical Spontaneous recovery of voiding should be watched for

Transurethral resection of the vesical neck is a valuable new method of treatment for neurogenic urinary retention Repeated resections may be necessary

The ultimate aim in treatment of the neurogenic bladder is the voiding of minimally infected urine without leakage or retention

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THE INDUCTION OF TRANSPLANTABLE BLADDER CARCINOMA IN INBRED STRAINS OF MICE[1]

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A principal difficulty in the study of carcinoma of the bladder has been that of consistently producing such lesions in a suitable experimental animal This problem's solution began in 1937 when Hueper and Wolfe first reported successfully inducing papillary tumors of the dog's bladder, both benign and malignant, when large doses of beta naphthylamine were fed by mouth [2] In 1943, Bonser[3] published the results of feeding a specially purified beta naphthylamine to 4 dogs over a period of from 3 to 5 years, and in this period observed histologic changes ranging from simple epithelial hyperplasia of the bladder to anaplastic carcinoma But by standards of time and expense, the dog is not a suitable experimental animal for the study of bladder cancer

Working with albino rats, Wilson, De Eds and Cox (1941)[4] found that of 39 rats fed 2-Acetylaminofluorene for 95 days or more, 10 developed carcinoma of the bladder Feeding the same carcinogen to the CBA strain of mice, Armstrong and Bonser (1944)[5] were successful in inducing malignant changes in the bladder epithelium of 4 mice out of 6 surviving 53 to 65 weeks of treatment Foulds (1947)[6] found only 25 weeks of feeding 2-Acetylaminofluorene to the R_3 strain of mice was necessary in developing epithelial tumors of the bladder, though the tumors required an additional period of from 14 to 59 weeks to become demonstrable About one half of his treated male mice developed such tumors but none occurred in the females

2 Acetylaminofluorene however, is not a specific bladder carcinogen, for malignant tumors also developed in other organs Furthermore, the induction of carcinoma of the bladder in the normally situated bladder of small experimental animals has the distinct limitations of time and space The limitation of time is that the individual tumor has only the life span of the experimental animal in which to grow The limitation of space is that imposed by the bladder in situ—the occurrence of carcinoma can scarcely be determined until autopsy after death or sacrifice of the animal

These limitations do not apply to a method we wish to describe in this report—a method in which carcinoma of the bladder has been induced in inbred strains of mice as a subcutaneous implant which continues its growth as a homologous subcutaneous transplant

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[1] Read at annual meeting American Association of Genito Urinary Surgeons, White Sulphur Springs W Va May 10 1949

[2] Hueper, W C and Wolfe, H D Am J Path , 13 656, 1937

[3] Bonser, G M J Path & Bact , 55 1, 1943

[4] Wilson, R H , De Eds F and Cox, A J Cancer Res , 1 595, 1941

[5] Armstrong, E C and Bonser, G M J Path & Bact , 56 507, 1944

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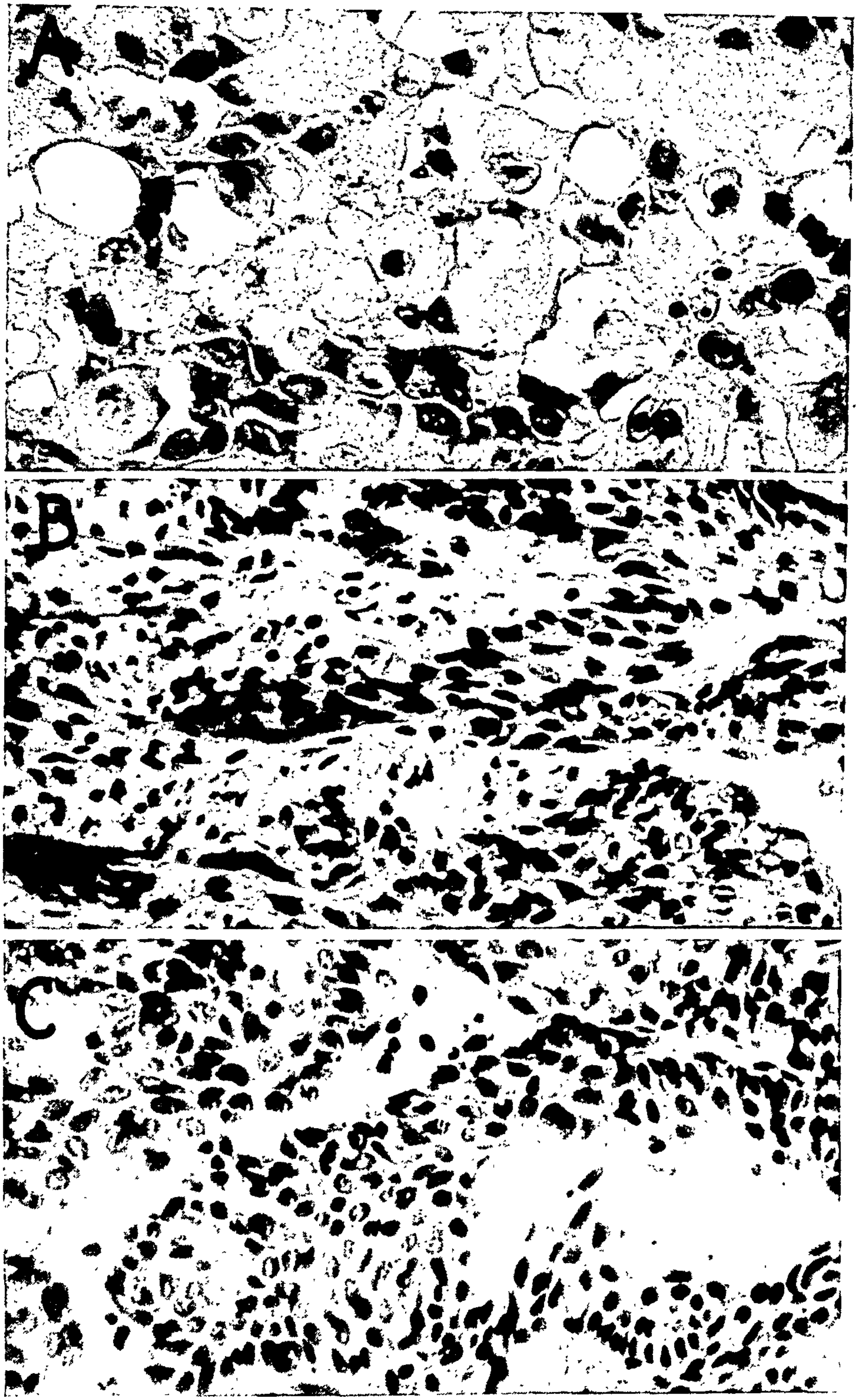

FIG. 1. *A*, tumor No. 32, C_3H mouse, third transplant generation (× 650); an undifferentiated carcinoma. *B*, tumor No. 148, C_{57} mouse, 4½ months after induction (× 400); papillary tongues of epithelial malignancy project into subcutaneous tissue of host. *C*, tumor No. 148, C_{57} mouse, 4½ months after induction (× 400); malignant cells have tendency toward papillary arrangement.

The first successful attempt to induce a series of transplantable tumors arising from adult tissue and capable of growing as homologous subcutaneous grafts was reported by Horning in 1946.[7] Horning induced and maintained by transplantation glandular carcinoma of the prostate gland in inbred Strong A mice. Our application of the Horning technique to the problem of inducing transplantable bladder carcinomata is described below.

The bladder is removed from a young mouse of an inbred strain and the entire mucosa, with portions of adherent submucosa, immediately dissected from the bladder wall under a dissecting microscope. This isolated mucosal layer, with its adherent submucosa, is wrapped around crystals of 20-methylcholanthrene, care being taken that only the epithelial portion of the mucosa comes into contact with the carcinogen; by means of a special trocar the mucosal wrapping thus produced is then implanted under the abdominal skin of a host animal from the same inbred strain—in our experiments, a litter mate. Sterile technique is maintained throughout.

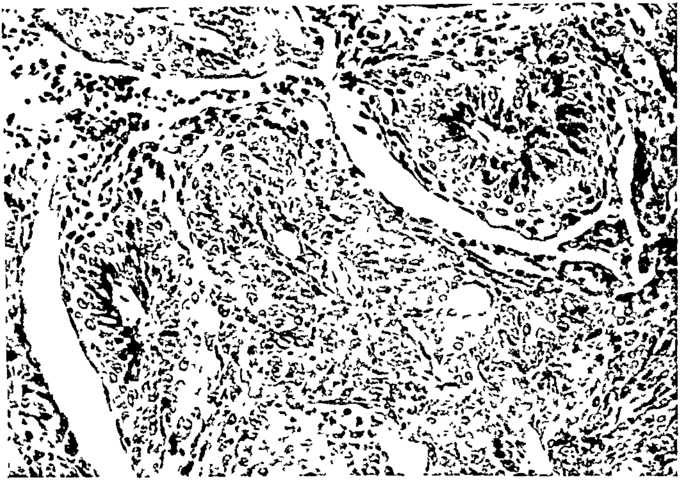

FIG 2. Tumor No. 148, C_{57} mouse, in its second transplant generation (× 400); squamous cells are well differentiated, showing keratin formation.

After the tumor has grown to transplantable size, it is excised, minced, and implanted subcutaneously into the desired number of mice from the same strain.

When carcinogens induce tumors by direct tissue contact the tumor type developed depends upon the nature of the tissue cell contacted. In our earlier work technical errors permitted the carcinogen to contact cells other than those of the bladder epithelium. This error resulted in sarcoma arising from the non-epithelial cells contacted, since in the mouse sarcomata are easier of induction and more rapid in their growth than carcinomata. These technical errors are not yet completely eliminated although the method is yielding a higher percentage of carcinomas as we become more proficient.

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[7] Horning, E S.: Lancet, 2: 829, 1946.

RESULTS

In this work we have used three inbred stains of mice. The Strong A strain yielded two carcinomas, both currently in their third transplant generation, from twenty-three attempted inductions. Our efforts in strain C_{57} were productive of only one transplantable carcinoma in 32 trials. In C_3H mice we achieved eleven transplantable carcinomas out of 65 attempts.

After the first transplantation there has been no change in the histologic pattern of these epithelial malignancies through as many as eleven transplant generations. In all strains, the development of the carcinoma in its host to transplantable size has required from two to four and one-half months. Sex, either of donor or host, has not appeared to influence development of the carcinomas.

SUMMARY

The Horning technique has induced and perpetuated in mice a constant type of epithelial bladder cancer beyond the life span of the individual experimental animal. It has brought carcinoma of the bladder to a readily accessible area beneath the skin where the influence of experimental variables may be easily measured. With refinements in technique making predictable an expected per cent of carcinomas, inquiry into inhibition of vesical carcinoma becomes feasible. The technique described offers an improved animal test object for investigation of carcinoma of the urinary bladder.

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We are also greatly indebted to Dr. Robert H. Clymer, Jr., to Mr. A. L. Bates, chief technical assistant, and to Miss Else Ask, technical assistant.

We also wish to thank Dr. Robert Horn for reviewing our histological sections.

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PHASES OF BLADDER CARCINOGENESIS IN MICE

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The induction of transplantable bladder carcinoma in inbred strains of mice has been the subject of another report.[1] These carcinomas have been grown successfully as homologous subcutaneous transplants through as many as 10 transplant generations. The purpose of this preliminary communication is to detail some of the cellular changes which occur as normal bladder epithelium becomes malignant.

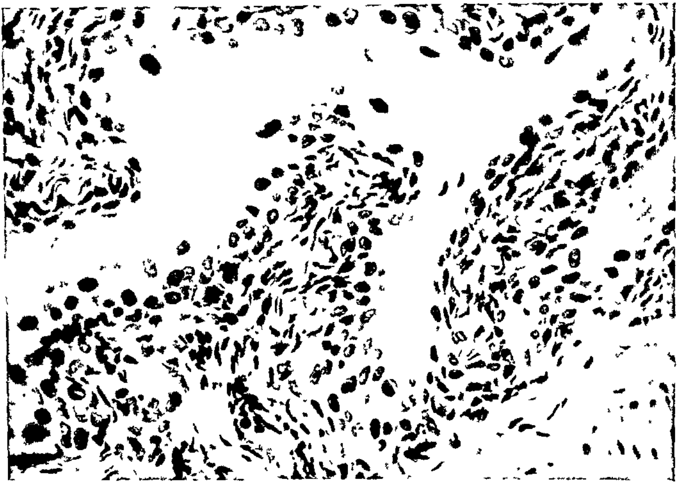


FIG. 1. High power view of normal mouse bladder

In brief, our technique for inducing bladder carcinoma in the mouse comprises excision of the mucosal layer from the bladder of a freshly sacrificed mouse and its immediate implantation, wrapped about 20-methylcholanthrene, into another mouse of the same inbred strain. The development of carcinoma in the subcutaneously implanted bladder mucosa has been followed serially by excising the implants at intervals and subjecting them to histologic study.

Thirty inbred C_3H mice were implanted with subcutaneous homologous grafts of bladder mucosa wrapped about 20-methylcholanthrene. Because we have seen no malignant tumor appear in less than 2 months after grafting, only mice which survived the initial 2 months after grafting were considered likely to show carcinogenic change. During the first 2 months 4 mice were sacrificed

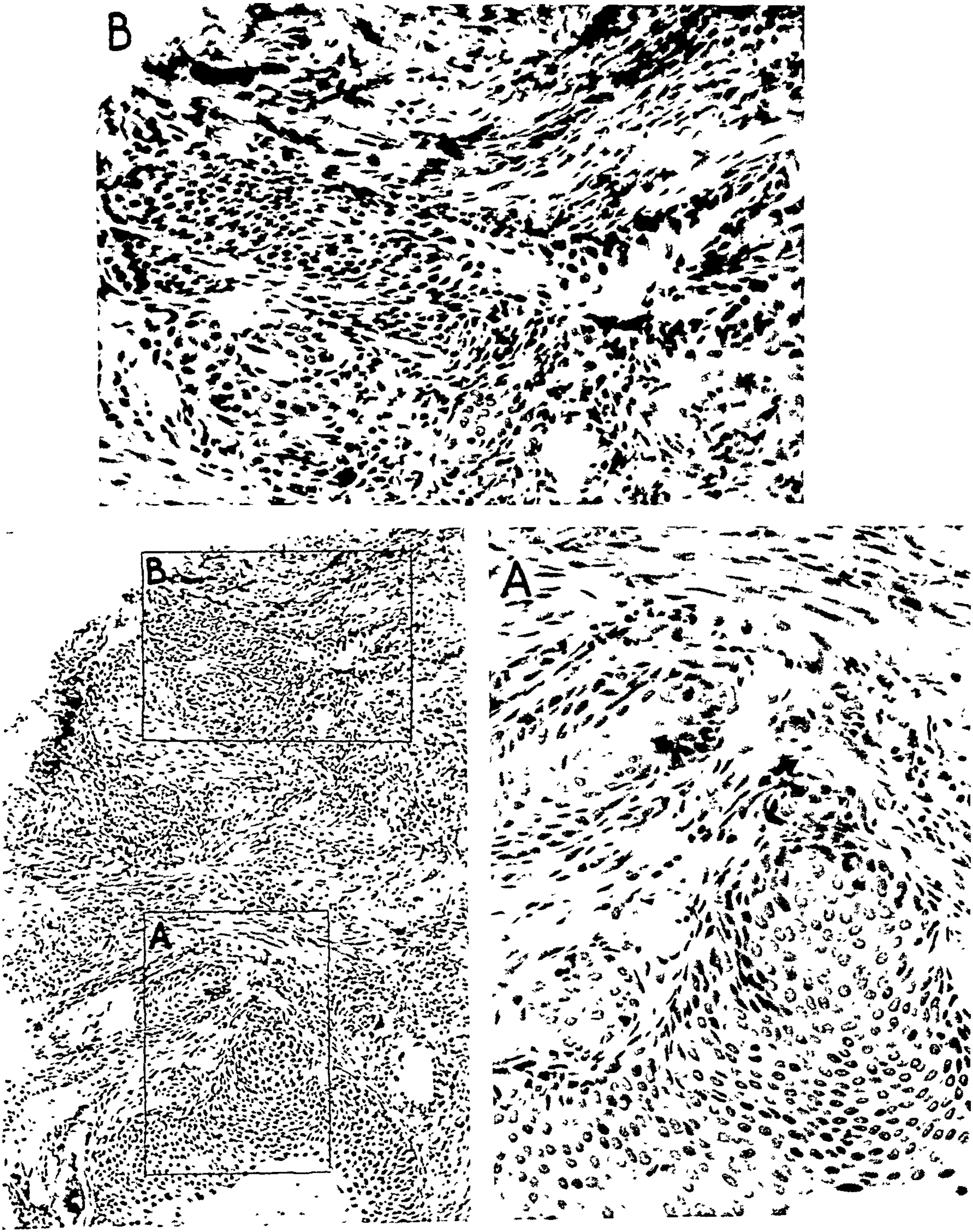
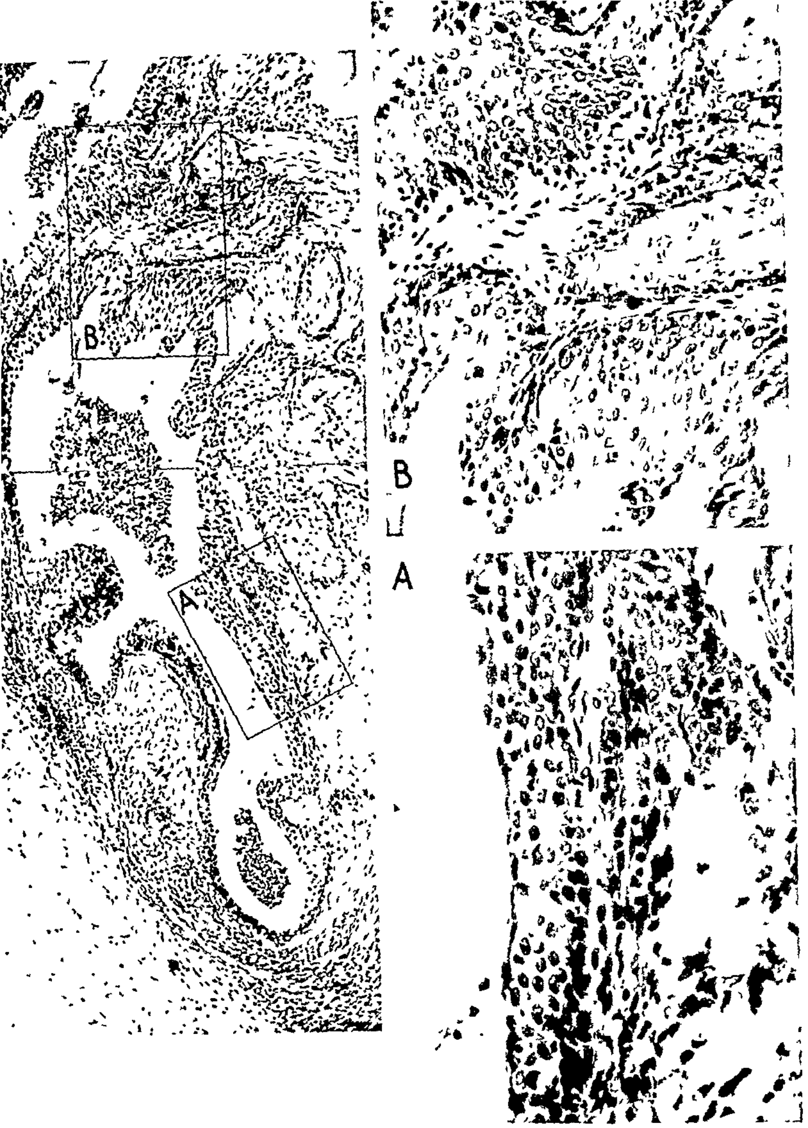


Fig. 2. Photomicrograph at lower left is low power view of implant, showing wall of cyst cavity, *A*, and well marked hyperplasia. In same photomicrograph, at *B*, remote from implant, are nests of epithelial cells which are probably malignant. Upper illustration, *B*, is high power of *B* in lower left photomicrograph. The lower right illustration, *A*, is high power view of *A* in lower left photomicrograph.



power view of implant demonstrating cyst
aft, perhaps due to heterozygous factors. In
lium that is nearly normal Some carcinoma
In *B* there is well marked squamous metaplasia and carcinoma in situ, which in upper left has invaded basement membrane Illustrations on right are high power views of *A* and *B* shown in lower left photomicrograph.

in order to study early adaptive changes in the graft and 6 mice died from adverse environmental factors. Of the 20 mice remaining, 4 developed histologic evidence of squamous cell carcinoma in from 2½ to 3½ months after grafting. Three sarcomas developed in a period of 4 to 6 months after the time of grafting. A few mice of other non-inbred strains were also grafted. In these the graft failed to maintain its viability except in 1 mouse (fig. 3) in which carcinoma developed.

The epithelium of the mouse's bladder is normally composed of transitional-like cells, covered over by a single layer of large, flat, multi-nucleated squamous-like cells which we have termed "covering cells". These "covering cells" have not thus far appeared to take part in carcinomatous change. See figure 1.

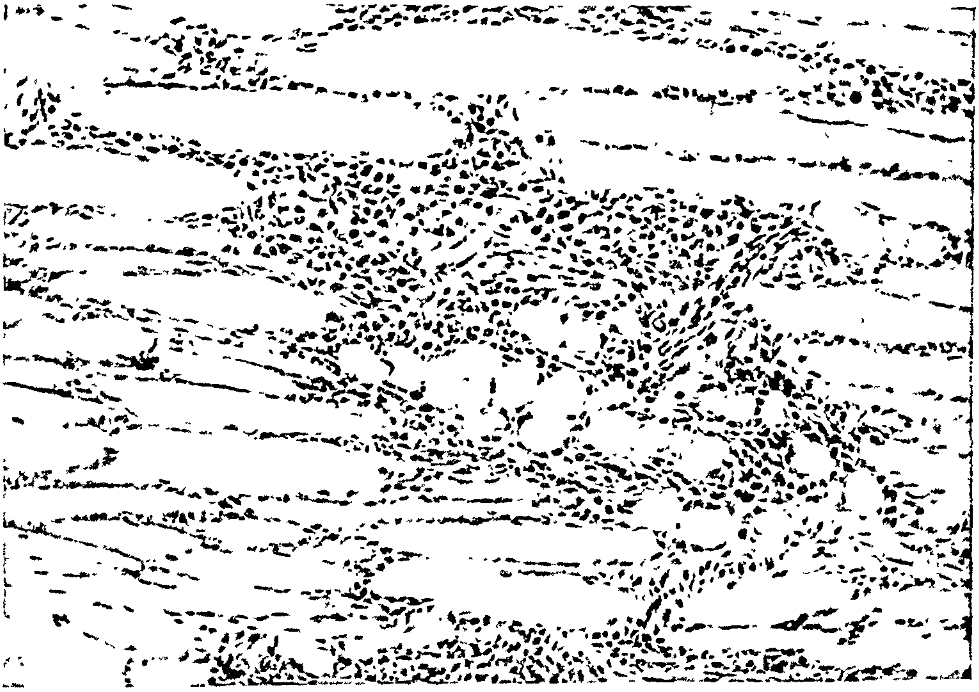


FIG. 4. Low power view, showing carcinoma that has invaded striated muscle of abdominal wall.

Within a few days a small cyst is formed by the homologous tissue at the site of implantation. The epithelial surface of the bladder mucosa taken from the donor mouse forms the lining of this cyst. The rest of the cyst wall is formed from the subcutaneous tissue of the host mouse by fibrous tissue reaction. The carcinogen lies within the cavity of the cyst in contact with the mucosal surface, though it does not always contact the entire mucosal surface due to irregularities in the contour of the cyst.

There has been no absolute uniformity in the progression of these cell changes which precede epithelial malignancy. In most cases however, hyperplasia, carcinoma in situ, and invasive carcinoma were felt to be sequential, though in fact all were sometimes demonstrable in the same preparation. These changes were observed over wide areas of epithelium and in no case was a focal spot of malignancy seen bordered by entirely normal mucosa. See figure 2.

In most cases, metaplasia to squamous epithelium developed coincidentally with malignant change in the epithelium. In some of our tumors however, the fact that metaplasia had occurred could be definitely established only after the first transplantation of the tumor when the differentiation of the carcinomatous cells certified their squamous nature. See figures 3 and 4.

We believe that the technique of inducing transplantable carcinoma of the urinary bladder in a subcutaneous locus offers opportunity for the study of this particular carcinogenesis in detail.

Acknowledgments: We wish to thank Dr. Margaret Reed Lewis and Dr. Robert Horn for their help and advice. We are deeply indebted to the Medical Research Foundation and its president, Mr. Lawrence E. Jones, for financial assistance.

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the conclusion of the procedure the mass overlying the right lateral lobe was still present on rectal examination, although the resection appeared adequate. The postoperative course was uneventful, the catheter being removed on the third day. The patient voided a good stream of clear urine without difficulty thereafter and had no residual urine.

Histological examination of the removed tissue was carried out by Dr. C. T. Ashworth, whose report we quote: "Microscopic examination of multiple sections of prostatic fragments shows a striking infiltration of small lymphocytes. The individual lymphocytes are small cells with a scanty rim of cytoplasm about a hyperchromatic nucleus. The infiltration is heavy in all areas. Scattered remnants of the fibromuscular stroma are noted, but these elements are separated and distorted by the infiltration. Scattered areas of prostatic glands are noted in the section wherein the glands are lined by tall columnar actively secreting epithelium. A few papillary enfoldings are noted. Neither the glandular elements nor the fibromuscular stoma are hyperactive or hyperplastic in appearance. Adenomatous hyperplasia is not judged to be present. In one area transitional epithelium of the urethra is noted and in the subepithelial tissues the infiltration is heavy as it is elsewhere. Pathological diagnosis: Lymphocytic leukemic infiltration of prostate." Microphotographs of these sections are shown in figure 1.

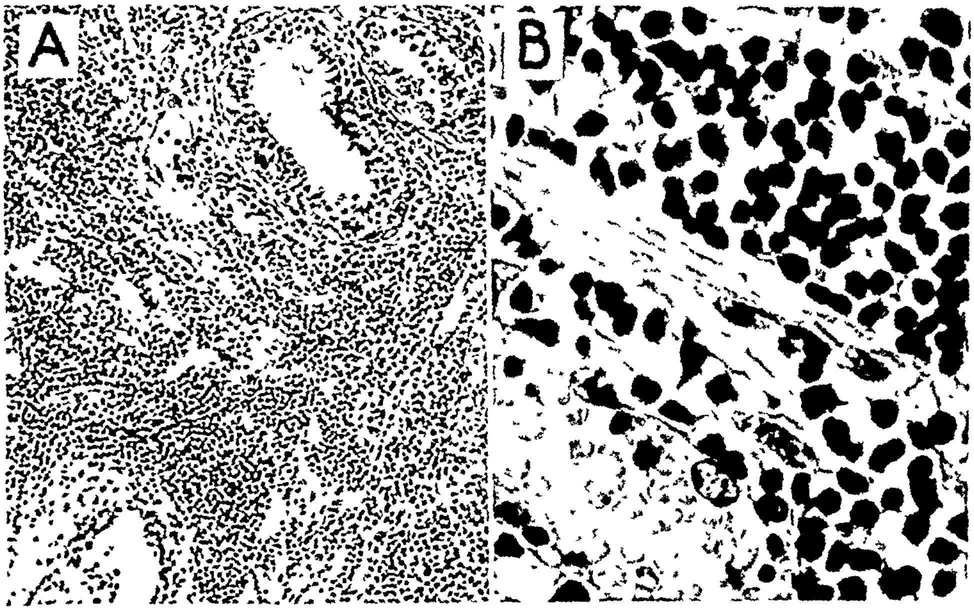

FIG 1 *A*, low power view of resected prostatic tissue, showing cellular infiltration *B* high power view of resected prostatic tissue, showing atypical lymphocytes.

Medical consultants, who concurred in the diagnosis of chronic lymphatic leukemia, started the patient on urethane 1.0 gm., t. i. d., 3 days after the operation on June 21, 1948. On the seventh postoperative day the patient was transferred to the medical service for further treatment of the blood dyscrasia. Forty-eight hours after institution of urethane therapy the white blood count was 51,250. The dose of urethane was then increased to 6 gm. a day, and the white count gradually fell until after 19 days of therapy it was 12,000 with 95 per cent lymphocytes. The dose was then reduced to 1.0 gm. daily. During the period on the medical service the temperature ranged from 101 to 103 F daily, with no discernible cause in the chest or urinary tract. Penicillin and sulfadiazine were given for this.

On the thirtieth hospital day the patient, whose condition was satisfactory except for the fever, suffered a severe epistaxis requiring transfusion of 500 cc of whole blood. The following day the patient's condition was critical. He bled from the gums and nose, was disoriented and lapsed into coma. Two additional transfusions were given, but he expired suddenly on the thirty-first day of hospitalization and 27 days after operation. There was no bleeding from the urinary tract. A white blood count on the day of death was 6,200 with 100 per cent lymphocytes.

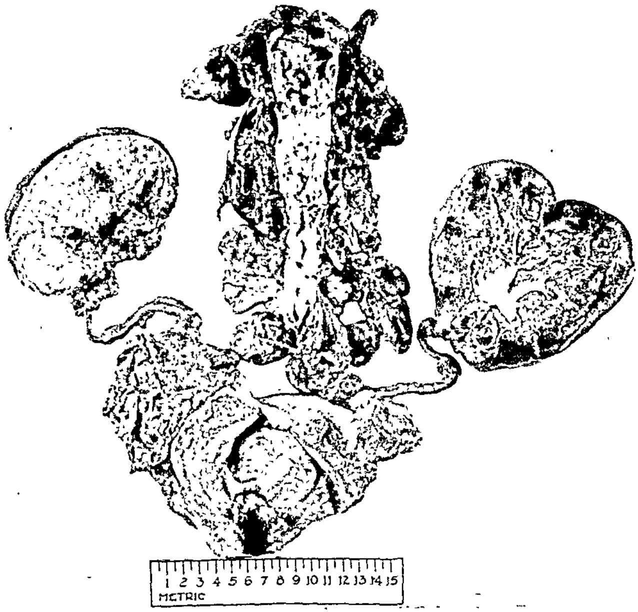

FIG. 2. Autopsy specimen of kidneys, ureters, bladder, prostate, abdominal aorta, and enlarged periaortic lymph nodes.

Complete autopsy was done with no obvious cause of death being ascertained on the gross examination. A photograph of the urinary organs is shown in figure 2. Further histological studies revealed complete replacement of the bone marrow with cells.

DISCUSSION

After a careful search of textbooks and journals, Jacobi, Panoff and Herzlich reported what they considered the first described example of bladder neck obstruction due to lymphatic leukemic infiltration of the prostate. They treated their patient by suprapubic prostatectomy with a good result.

A similar case was reported by McCrea in 1940, also treated by suprapubic prostatectomy.

Escue reported vesical neck obstruction in a woman, proven first by biopsy, due to infiltration with the cells of lymphatic leukemia. She was first treated by urethral dilatation, but when her symptoms recurred about eleven months later, tissue was removed with the resectoscope, and the diagnosis was again confirmed histologically.

Monocytic leukemia has likewise produced this same symptom picture. This has been described by Flaherty, Cope and Shecket, who treated their patient by transurethral resection; and by Lubin, Fetter and Erf, who did a suprapubic prostatectomy when they found they could not get a resectoscope through the urethra of their patient.

SUMMARY

Vesical neck obstruction due to leukemic infiltration of the prostate is a rare condition. We present a case treated by transurethral resection with complete alleviation of urinary symptoms. This is the third known case of lymphatic leukemic infiltration of the prostate causing obstructive uropathy.

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BLOOD LOSS IN PROSTATECTOMY

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Hemorrhage is a major cause of mortality and morbidity in prostatic surgery, but during the last decade the increasing availability of whole blood for transfusions has rendered the problem less troublesome Since the beginning of prostatic surgery numerous devices and methods for hemostasis have been advocated, and modifications are being introduced with such frequency as to indicate the concern among urologists for the problem

Numerous articles have advocated the use of various methods of hemostasis in prostatic surgery, but with a single exception references to hemorrhage have been only estimates and often grossly inaccurate Conclusions reached by such an unscientific approach are likely to be unsound

The material comprising this study consists of 100 prostatectomies The cases are unselected and are consecutive except for the exclusion of all but 20 cases of transurethral prostatectomies Each of the standard methods of prostatectomy has its special indications, and all are employed in this series and blood loss of each reported Because of the numerous methods of hemostasis advocated in suprapubic prostatectomy, a comparison of the various hemostatic agents is made

The technique employed in the determination of blood loss of the cases reported herein is not intended for routine use as it is quite time consuming Two factors are involved the collection of the blood which is lost, and the estimation of the hemoglobin of the specimen The method of collection differs according to the type of prostatectomy, while the hemoglobin determination remains the same for all

In transurethral prostatectomy it is necessary to collect and save the irrigating fluid used during the operation and to collect the urine of the patient until it is free of blood In the other types of prostatectomy the collection of the blood is more involved During the operation all sponges and drapes which contain blood are carefully placed in clean water and saved until the termination of the operation, when all the hemoglobin is manually removed therefrom

The blood or hemoglobin collected is diluted sufficiently to be read on a standard Klett Photelometer and a specimen of the fluid alkalinized with ammonium hydroxide It is then placed in the photelometer and the actual hemoglobin content determined The total diluted volume is known, and by a simple calculation the total amount of hemoglobin lost can be determined By dividing the patient's hemoglobin per 100 cc of blood into the amount of hemoglobin lost at the operation, the actual blood lost at operation is determined

In each case whether transurethral or otherwise, the blood loss determinations are continued until hematuria and bleeding from the wound have ceased

TRANSURETHRAL RESECTION

The amount of blood loss during and following transurethral prostatectomy depends upon a number of factors. The dexterity and ability of the surgeon are the major factors. The amount of tissue removed and the time consumed in the procedure determine to some degree the amount of hemorrhage which occurs. Inflammation of the prostate increases its blood supply and bleeding is increased. Finally it has been noted that in general, carcinoma of the prostate bleeds less profusely during resection than hyperplasia of the prostate.

TABLE 1. *Transurethral resection*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Fibrosis	4	20
Hyperplasia	14	78
Fibrosis	7	130
Acute and chronic prostatitis	6	1310
Hyperplasia	8	45
Carcinoma	18	380
Hyperplasia	12	300
Hyperplasia	10	90
Hyperplasia	12	120
Hyperplasia	15	200
Hyperplasia	10	365
Hyperplasia	17	120
Hyperplasia	36	390
Hyperplasia	14	640
Hyperplasia	13	300
Hyperplasia	25	250
Hyperplasia	16	105
Hyperplasia	10	70
Hyperplasia	12	170
Carcinoma	14	60
Avg	14	260

In this series of cases only those patients with glands whose estimated weight was 40 gm. or less were resected, while all others were operated upon by one of the other several methods. The average blood loss was 260 cc, most of which occurred during the actual surgery. Few patients lost any appreciable amount of blood except for the first few postoperative hours. No case of secondary hemorrhage was encountered. See table 1.

SUPRAPUBIC PROSTATECTOMY

There are countless variations of this operation and many different methods of hemostasis. Four popular types were chosen for this study and a comparison of the effectiveness of the hemostasis is made. Twelve cases were operated upon without any method of hemostasis and serve as a control group. In these cases the bladder was drained following surgery by a cigarette drain and no effort whatever was made to stop the bleeding in the prostatic fossa. The average blood loss in this control group was 368 cc. See table 2.

Another group of cases was operated upon using a plain gauze pack in the prostatic fossa for hemostasis. The pack was composed of gauze, 1 inch wide and several feet in length. The pack was placed snugly in the fossa with one end extending from the inferior angle of the wound. A cigarette drain was used to drain the bladder. The blood loss in this group averaged 510 cc. See table 3.

TABLE 2. *Blood loss in suprapubic prostatectomy without hemostasis (control)*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Hyperplasia	47	600
Hyperplasia	110	790
Hyperplasia	24	130
Hyperplasia	39	370
Hyperplasia	77	190
Hyperplasia	60	325
Carcinoma	52	185
Hyperplasia	26	440
Hyperplasia	41	190
Hyperplasia	30	305
Hyperplasia	70	290
Hyperplasia	26	190
Avg	51	368

TABLE 3. *Blood loss in suprapubic prostatectomy using gauze pack in prostatic fossa as method of hemostasis*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Hyperplasia	25	205
Hyperplasia	15	560
Hyperplasia	198	435
Hyperplasia	32	160
Hyperplasia	188	1025
Hyperplasia	25	690
Avg	80	510

Oxidized gauze and similar absorbable hemostatic agents are being used with increasing frequency and form the basis of hemostasis for a third group of cases. The oxidized gauze was placed around a Foley catheter by threading the gauze over the end of the catheter, inflating the bag proximal to the gauze, and pulling the gauze-coated bag into the prostatic fossa. Traction was not applied. The average blood loss in this group was 210 cc. See table 4.

The most popular method of hemostasis in suprapubic prostatectomy in past years and perhaps at present is the Pilcher hemostatic bag or a similar device.

The method has many disadvantages which have been tolerated on the basis that the device was an effective hemostatic agent. The bag is quite painful for the patient and causes disruption of the wound in its removal. In addition it increases the possibility of infection, and unquestionably prolongs hospitalization considerably. Instead of being a hemostatic agent in this series, the method appears to cause bleeding to almost twice that in the control group. The patients lost an average of 630 cc of blood when this method was employed. See tables 5 and 6.

TABLE 4. *Blood loss in suprapubic prostatectomy using oxidized gauze pack in prostatic fossa as method of hemostasis*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Hyperplasia	105	260
Hyperplasia	60	175
Hyperplasia	24	185
Hyperplasia	20	265
Hyperplasia	60	105
Hyperplasia	42	310
Hyperplasia	58	160
Carcinoma	34	215
Avg	50	210

TABLE 5. *Blood loss in suprapubic prostatectomy using Pilcher (hemostatic) bag as method of hemostasis*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Hyperplasia	44	820
Hyperplasia	92	625
Hyperplasia	142	895
Hyperplasia	36	720
Hyperplasia	81	945
Hyperplasia	30	565
Hyperplasia	56	445
Hyperplasia	50	380
Hyperplasia	20	310
Carcinoma	72	575
Avg	62	630

RETROPUBIC PROSTATECTOMY

This method of prostatectomy has been fairly recently introduced and is enjoying increasing popularity. Its chief advantage is rapidity of healing and return of proper voiding. A far shorter period of hospitalization and convalescence is necessary as compared to suprapubic prostatectomy. One of the alleged advantages of the operation is that the prostatic vessels are isolated and ligated, allowing less bleeding than other methods. Our study of the method leads to the conclusion that this advantage is dubious since the patients lost more blood than in other methods when the vessels are not ligated. The average blood loss for 20 cases was 640 cc. See table 7.

TABLE 6. *Average blood loss in suprapubic prostatectomy with various methods of hemostasis*

METHOD OF HEMOSTASIS	AVERAGE WEIGHT OF TISSUE REMOVED	AVERAGE BLOOD LOSS
None, control	51	368
Gauze pack	80	510
Oxidized gauze pack	50	210
Pilcher bag	62	630

TABLE 7. *Blood loss in retropubic prostatectomy*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Hyperplasia	35	650
Hyperplasia	43	720
Hyperplasia	44	575
Hyperplasia	95	610
Hyperplasia	22	620
Hyperplasia	77	755
Hyperplasia	59	640
Hyperplasia	38	420
Hyperplasia	29	330
Hyperplasia	70	930
Hyperplasia	153	460
Hyperplasia	19	990
Hyperplasia	37	510
Hyperplasia	29	860
Hyperplasia	34	410
Hyperplasia	48	395
Hyperplasia	40	420
Hyperplasia	23	810
Hyperplasia	66	440
Carcinoma	33	1310
Avg.	50	640

PERINEAL PROSTATECTOMY

The approach to the prostate gland through the perineum for the enucleation of hyperplasia or for the radical removal of carcinoma has merit and advantage well known to all. A series of each type is included in this study. In simple or conservative perineal prostatectomy the patient lost an average of 458 cc of blood, while in radical perineal prostatectomy the blood loss was 918 cc. In both the standard approach described by Young was used. See tables 8 and 9.

TABLE 8. *Perineal prostatectomy, simple*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Hyperplasia	35	555
Hyperplasia	44	1400
Hyperplasia	110	340
Hyperplasia	113	310
Hyperplasia	92	280
Hyperplasia	44	285
Hyperplasia	75	595
Hyperplasia	43	455
Hyperplasia	72	740
Hyperplasia	75	280
Hyperplasia	55	460
Hyperplasia	84	510
Hyperplasia	71	425
Hyperplasia	38	190
Hyperplasia	44	165
Hyperplasia	32	350
Hyperplasia	145	460
Avg	62	458

TABLE 9. *Radical perineal prostatectomy*

TISSUE REMOVED	WEIGHT	BLOOD LOSS
	Gm.	*cc*
Prostatitis	35	750
Carcinoma	37	750
Carcinoma	26	955
Carcinoma	23	915
Carcinoma	28	910
Carcinoma	30	730
Carcinoma	80	1460
Avg	37	918

DISCUSSION

Blood loss cannot be determined by a casual appraisal of blood soaked linen following surgery. The advocacy of methods and devices for prostatectomy based upon such vague and inaccurate estimations is not justified. In this series an estimation was made in each case and compared with the actual blood loss, and variations of 100 per cent were commonly noted.

Although not included in the tables, special attention was given to the relation of blood pressure, age, and bleeding tendencies to blood loss at prostatectomy. No correlation was noted.

In the study of blood loss at prostatectomy, it appeared advisable to consider the behavior of the prostatic cavity following removal of the hypertrophied gland.

This has received very little attention in the literature. The findings reported herein are based upon actual observations at the operating table and further study by urethrocystograms, made immediately postoperatively and at 6, 12, and 24 hour intervals thereafter.

The vesical neck contracts within a few minutes after prostatectomy to its normal size (26–30 F). The prostatic fossa likewise contracts immediately to some degree, but not so markedly as the vesical neck. The cavity remaining after enucleation is not conical, but is fusiform, being dilated in the midportion and narrow at the vesical neck and urinary sphincter. The initial contraction of the prostatic fossa is approximately 50 per cent, and within the next 6 to 12 hours there is another reduction in size of approximately 25 per cent. After this period, the contraction of the fossa proceeds gradually until completion.

This behavior of the prostatic cavity appears to have an important relation to blood loss. The principal blood supply to the prostate enters in the region of the vesical neck, being divided into two groups, the urethral and the capsular. It is well established that as hyperplasia progresses, the urethral division of the arterial supply becomes predominant. Thus, after prostatectomy the major source of bleeding is in the region of the vesical neck rather than throughout the dilated cavity. The contraction of the bladder neck and prostatic fossa is an important factor in allowing the torn vessels to cease bleeding. Any hemostatic method or device which interferes with this contraction may be ineffective.

A pack which fits the cavity at the time of operation becomes too large within a few hours and prevents normal contraction. Other pressure devices such as the Pilcher bag interfere severely with the resumption of the normal size of the vesical neck. In this series, both the pack and the Pilcher bag were associated with considerably more bleeding than the control group in which no hemostatic device was used. The method associated with the smallest blood loss was the use of oxidized gauze placed around the bag of a Foley catheter inflated with 6–8 cc of water placed in the prostatic fossa without traction.

SUMMARY AND CONCLUSIONS

Blood loss was measured in 100 prostatectomies.

Average blood loss was as follows:

a) Transurethral resection, 260 cc.
b) Suprapubic prostatectomy:
    1) Control group (no hemostatic device), 368 cc.
    2) Gauze pack, 510 cc.
    3) Oxidized gauze pack with Foley catheter, 210 cc.
    4) Pilcher bag, 630 cc.
c) Retropubic prostatectomy, 640 cc.
d) Perineal prostatectomy
    1) Simple, 458 cc.
    2) Radical, 918 cc.

Many patients lose sufficient blood during prostatectomy to require replacement by transfusion. This is especially true in radical perineal prostatectomy.

Factors influencing blood loss:

a) The skill of the surgeon is of paramount importance in the control of hemorrhage in all types of prostatectomy, but especially in transurethral resection.
b) The amount of tissue removed at prostatectomy is unrelated to blood loss except in the transurethral type.
c) Hypertension and arteriosclerosis do not increase blood loss.
d) Inflammation of the prostate increases hemorrhage at prostatectomy.

The use of oxidized gauze or similar absorbable material in conjunction with a Foley catheter allowed the least hemorrhage in suprapubic prostatectomy in this series.

The effectiveness of the Pilcher bag as a hemostatic device is questioned.

Although retropubic prostatectomy is an excellent method, the control of hemorrhage should not be considered as one of its advantages.

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PERINEAL TESTICLE

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A perineal testicle is a condition which is extremely rare. The last case reported was one by Cecil who stated it was the one hundred and fourth case on record. We wish to record in this review another instance of this condition in a patient on whom we operated recently, and thus bring the total number of reported cases to 105.

An exhaustive study of the perineal testis was made in 1905 by Klein. He found that the testis, when in the perineum, practically always occupies the same position. This is between an imaginary line in front passing behind the root of the scrotum and a similar line passing in front of the anus. Laterally, it is outside the line of raphe. The testicle never has been known to lie behind the bi-ischiatic line which passes anterior to the anal orifice. Usually it is found with its longitudinal axis directed anteroposteriorly; sometimes it lies obliquely with its anterior end pointing outward and its posterior end inward. The gland is superficial, the skin over it presenting a perfectly normal appearance, without tension. No adhesion of the testis to the tissue covering it has been observed. Frequently, it can be moved about with ease. Ledwich in 1855, during a necropsy of a 35 year old man, found a perineal testicle which could be forced upward and forward into the scrotum, but readily returned to its former position.

The asymmetrical appearance of the scrotum is characteristic. The condition being unilateral, one pouch is normal, while the other is reduced in size, atrophic, and frequently rudimentary.

The perineal testicle is an ectopic one. When a testicle is arrested along its normal course of migration, the condition is the common one of cryptorchidism. When it migrates away from its normal course of descent, the condition is the rare one of ectopia.

There are five varieties of ectopia of the testicle:

1) Superficial, inguinal or interstitial. In these types the testis, after leaving the external ring, passes upward and outward toward the anterosuperior spine of the ilium and comes to rest upon the aponeurosis of the external oblique. This is the most common form of ectopia.

2) Pubo-penile. The testis is found at the dorsum of the base of the penis overlying the pubic bone.

3) Femoral or crural. The testicle occupies a position in Scarpa's triangle on the medial side of the thigh.

4) Transverse. Both testes pass down the same inguinal canal and come to lie in the same scrotal sac.

5) Perineal. Testicle is found in the perineum.

John Hunter was the first to describe the perineal testicle. He reported 2 cases in 1786. Hunter gave the name of gubernaculum to the structure he believed to be responsible for causing the descent of the testis.

The next mention found of perineal testis was by Ricord who reported 2 cases in 1843 Vidal observed 2 cases in 1846 Ledwich in 1855 reported his observation of perineal testis in a man 35 years of age

Curling in 1857 was the first to operate on this condition The patient was an infant 4 weeks of age The patient died of sepsis

Godard in 1856 reported the case of a man 58 years old who had a swelling in his left groin After he had worn a truss for 25 years, the testicle finally came to rest in the perineum

The second surgeon to operate was Partridge (1858) and the third James Adams (1871) Both operations resulted in sepsis, and the patients died

The first successful operation for perineal testicle was carried out by Annandale in 1879 In 1899 Weinberger reported that by that time 74 cases had been placed on record When Klein wrote his important thesis on the subject in *1906*, he included 2 cases and the total number reached 81

Campbell in 1937 was able to find in the literature 102 cases Jones and Lieberthal in 1938 reported what they stated to be the one hundred and third case They found that only 22 cases had been reported in the previous 32 years Cecil in 1947 reported the one hundred and fourth case

The case we wish to present is the one hundred and fifth one for record

CASE REPORT

D C P , No 162510, an 18 year old male, complaining of a misplaced testicle, was admitted to Barnes Hospital on August 17, 1948 His general health always had been excellent, he never had had any serious illnesses or mumps Only recently had the perineal testicle caused any discomfort, this discomfort being present during some athetics at school He did not ride a bicycle or horse

Physical examination revealed a well developed young man with normally developed secondary sexual characteristics The external genitalia were well developed and normal except for the left side of the scrotum which was rudimentary

The left testicle was found in the left perineum (fig 1, A and B) It was located to the left of the raphe of the perineum and above the ischial tuberosity The testicle was approximately normal in size, non tender, not firmly fixed, but could not be pushed up to the scrotum

At operation an incision was made over the perineal testicle extending upward between the scrotum and thigh to the junction of the scrotum and groin The testicle was freed easily by blunt and sharp dissection The tunica vaginalis was opened and found to contain approximately 25 cc clear fluid The tunica vaginalis extended up the cord almost to the external ring, but no opening was found to extend to the peritoneal cavity The tunica vaginalis was everted to correct small hydrocele

A small biopsy specimen of the testicle was taken and was reported (fig 2) *testis hypoplasia*

Using the finger for blunt dissection, a place was made for the testicle in the scrotum Achromic 1 suture was passed through the gubernaculum and both ends

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RESULTS OBTAINED IN TREATING GENITO-URINARY TUBERCULOSIS WITH STREPTOMYCIN[1]

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The wealth of material in the medical literature on the discovery and development of streptomycin therapy, and its action in vitro and in experimental animals, indicates the tremendous interest manifested in this antibiotic. Its discovery followed closely that of penicillin. When it was found that the sulfa drugs exerted an inhibitory influence on the growth and activity of the Mycobacterium tuberculosis, it was natural that the scientific mind should seek for a substance which would tend to arrest the disease itself. The need for a specific drug to assist in combating human tuberculosis is a stimulating one. After the slight, but definite deterrent action of sulfanilamide on tuberculosis was observed, investigators were prompted to experiment with many of the sulfanilamide derivatives. When the sulfone compounds became available in 1939,[2] the first to be tested in both experimental and clinical tuberculosis was promin. Later diasone[3] and promizole[4] were also employed. Finally, streptomycin, a fungus extract, isolated by Schatz, Bugie and Waksman, in January 1944,[5] was found to exert a marked therapeutic effect on experimental tuberculosis in guinea pigs. It was given a clinical trial by Hinshaw and Feldman in the autumn of 1944. Since then the drug has been employed in all forms of clinical tuberculosis. It is now possible for the first time to arrest the course of several different clinical types of potentially fatal tuberculosis by specific chemotherapy.[6]

Up to the present time we have not used combined promin and streptomycin in the treatment of human tuberculosis, or the chaulmoogra oil-streptomycin therapy advocated by Slotkin.[7] Our cases receiving streptomycin with PAS are too recent to report.

Since reports on the pharmacology and other aspects of the drug are readily available, I shall not duplicate them here.

Before proceeding further, certain fundamental principles should be emphasized:

1) We never speak of a cure in a case of tuberculosis, cancer, leprosy or syphilis after a few months or even years of treatment. Arrest of the disease is

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[1] Read at annual meeting. American Urological Association, Boston, Mass. May 18, 1948.

[2] Feldman, W. H., Hinshaw, H. C. and Moses, H. E.: Effect of promin on experimental tuberculosis: Preliminary report. Proc. Staff Meet., Mayo Clinic, 12: 695, 1940.

[3] Feldman, W. H., Hinshaw, H. C. and Moses, H. E.: Effects on experimental tuberculosis of 4, 4-diaminodiphenylsulfone. Am. J. Med. Sc., 207: 290, 1944.

[4] Feldman. W. H., Hinshaw, H. C. and Mann, F. C.: Promizole in tuberculosis. Am. Rev. Tuberc., 50: 418, 1944.

[5] Schatz, A., Bugie, E. and Waksman, S. A.: Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. Proc. Soc. Exper. Biol. & Med., 55: 66, 1944.

[6] National Research Council—Report of Committee on Chemotherapeutics and other agents; the effects of streptomycin on tuberculosis in man. J. A. M. A., 135: 634, 1947.

[7] Slotkin, G. E.: A new and rapid method for the control of urinary tuberculosis: preliminary report. J. Urol., 58: 464–478. 1947.

still the expression of choice in evaluating results from streptomycin therapy and relapses on the same basis and causes as found previously with other methods of treatment are to be expected

2) We must not conclude that streptomycin has a different effect on tuberculosis from that of any other anti microbial agent on other infections Hinshaw and Feldman originally described the action of streptomycin as "suppressive" and commented as follows "What we should anticipate from streptomycin and future anti-tuberculous agents is not a dissolution of all tubercle bacilli within the body, but rather the conversion of all, or nearly all, cases of certain types of active tuberculosis into the equivalent of the best results obtained by natural mechanisms "[8]

3) The rather rapid development of resistance of the tubercle bacillus to streptomycin is most interesting, but also very discouraging, especially in a disease so chronic in nature

We have 1 patient resistant to 200 mcg streptomycin after the second week of treatment Nevertheless all bladder ulcerations have disappeared and this patient is clinically free from symptoms, after 90 days continued treatment of 1 gm per day

Demeree, as quoted by Silbie, in 1946,[9] stated. "One of the most serious obstacles to the achievement of maximal therapeutic benefits from streptomycin in clinical tuberculosis is the problem of streptomycin-resistant tubercle bacilli and although the problem of drug resistant micro organisms is not entirely understood, there is evidence that this phenomenon represents a selective process dependent on the capacity of bacteria to undergo spontaneous variation or mutation "

It is well known that the human body is very resistant to the tubercle bacillus Therefore, in clinical tuberculosis the appearance of laboratory-resistant bacilli may not necessarily indicate that the predominant bacterial population is streptomycin resistant The finding of a streptomycin-resistant strain in vitro should not necessarily persuade us to discontinue further therapy as long as active pathology is still present, and clinically the patient is improving No sensitivity test so far devised includes the patient's antibodies

4) Streptomycin should be used in combination with other accepted, effective methods of treatment, rather than as a substitute for such proved therapeutic procedures as sanatorium care and surgery In our experience it has been most successful when used in conjunction with surgery

STREPTOMYCIN THERAPY IN PREVIOUSLY INOPERABLE GENITO-URINARY TUBERCULOSIS

Tuberculous lesions of the kidney without involvement of the lower urinary tract and genital organs are rarely encountered In addition Medlar[10] claims that unilateral tuberculosis of the kidney merely represents the end result of a previous widespread infection of both kidneys. This would mean, therefore, that in some cases the so-called healthy kidney has healed. With the advent of streptomycin we now have an agent to control the reactivation of the disease in this healed kidney and any concomitant disease process in the lower urinary tract.

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[8] Feldman, W H , Hinshaw, H C and Mann, F C Streptomycin in experimental tuberculosis Am Rev Tuberc 52 269, 1945

[9] Feldman W H , and Hinshaw, H C Brit Med J No 4541, p 91 1948

[10] Medlar, E M and Sasano, K T Promin in experimental tuberculosis in the guinea pig Am Rev Tuberc , 47: 618, 1943

In pulmonary tuberculosis streptomycin has demonstrated its ability to heal minimal lesions rapidly. Clinical substantiation of this statement as applied to renal tuberculosis is found in 3 of our patients subjected to nephrectomy. In each instance a kidney with a demonstrable pyelographic lesion was removed. The opposite kidney was found to yield acid-fast bacilli on smear and culture of the urine, but no lesion was ever demonstrated in pyelograms. These patients were given 1 gm. streptomycin daily for 8 weeks prior to surgery, during which time the urine from the kidney which was not to be removed became negative. After removal of the more diseased kidney, streptomycin therapy was continued for 30 to 60 days without a positive urine from the remaining kidney. One patient is now 13 months postoperative, another is 9 months and the third one 6 months. We cannot yet say that the disease has been permanently arrested. However, in a paper read before the Southeastern Section of the American Urological Association, in 1942,[11] I stated that my results had been uniformly unsuccessful in this type of case and consequently I had abandoned nephrectomy almost entirely if contralateral disease was found on smear or culture.

In another case in which no surgery was performed a most remarkable result was obtained with streptomycin: apparent healing of a typical cavitation in the right kidney and conversion of the urine from the left kidney from positive to negative. In this instance operation was not done because of complications which made this patient a poor surgical risk.

All of our cases, whether unilateral or bilateral disease exists, are given at least 3 weeks preoperative streptomycin therapy followed by postoperative administration of the antibiotic. In no case have we had a postoperative opening of the wound.

We have established the following diagnostic criteria when instituting treatment for renal tuberculosis with either surgery or streptomycin therapy, or both: 1) a definite pyelographic lesion; 2) a positive culture of the tubercle bacillus from urine obtained at cystoscopy, with or without pyelographic proof; and 3) in some instances where there is impairment of unilateral kidney function, with the presence of tubercle bacilli in bladder specimen.

Many valuable adjuncts have evolved as aids in accurate diagnosis, especially the newer rapid culture media.[12] We have found it most satisfactory to precede the administration of streptomycin with a week or 10 days of penicillin and sulfadiazine to eliminate the mixed organisms which so often kill the guinea pig or overgrow the tubercle bacillus in cultures.

Since we are mainly concerned with the results of streptomycin therapy in genito urinary tuberculosis, and inasmuch as the subject of resistance and sensitivity has been thoroughly investigated by Hinshaw, Feldman and others, we shall merely define our criterion of "resistance"

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[11] Huffines, T. R.: Surgical treatment of urogenital tuberculosis. J. Urol., 49: 184–186, 1943.

[12] Fisher, M. W.: Streptomycin resistant tubercle bacilli; their development during streptomycin therapy of pulmonary tuberculosis. Am. Rev. Tuberc., 57: 53–57, 1948.

We consider an organism streptomycin-sensitive if it fails to grow in 1–10 micrograms of streptomycin per cubic centimeter If it does grow in a concentration above 10 micrograms, we consider it streptomycin-resistant

We used this 10 *microgram figure as our point of optimum therapy*, because this is the average maximum blood level obtainable with the 1 gm or 2 gm daily dosage of streptomycin

TOXICITY

The question of the toxic reactions in streptomycin therapy has been widely discussed in the current literature, and I shall merely *mention the most frequently* encountered: 1) severe exfoliative dermatitis, 2) impaired renal function and irritation, 3) toxic psychosis, 4) casts in urine, 5) stomatitis (we have had one from 1 gram daily dosage), 6) herpes, 7) recurrent vertigo, 8) deafness, 9) fever, 10) eosinophilia, 11) monocytosis

Recently we have found that the administration of an anti histaminic along with streptomycin in cases that show the above reactions has permitted us to continue streptomycin even in the most sensitive cases We are also running a series of skin tests on the different trade brands of streptomycin and it has proved most interesting

However, since the dosage has so generally been reduced from 2 gm daily to 1 gm and in sinus cases to 0 2 gm , reactions are less frequent

An observation made by the Streptomycin Committee was that fewer doses during the day produced fewer toxic reactions Dr Emil Bogen, at the Streptomycin Conference, in St Louis, in October 1947, made a definite contribution in his statement that "the therapeutic effects of streptomycin are a function of peak blood levels attained, whereas the toxic effects of the drug appear to be a function of the average blood level attained over lengthy intervals "[13]

Alkalinization of the urine has aided in counteracting the renal toxic complications, such as the formation of casts Practically no work has been done to date about regulating dosage on the basis of weight of the patient Our future studies will be directed toward this end

In the early use of streptomycin a good many of the toxic symptoms and undesirable reactions were caused by impurities in the streptomycin preparation But the toxicity today in the use of the calcium complex leaves only the toxicity which is inherent in the drug itself or in the diluting agent

EFFECT OF STREPTOMYCIN IN THE HEALING PROCESS

Very little has appeared in the literature on the mode of healing of tuberculous lesions under streptomycin treatment, and especially as far as the kidneys are concerned Those lesions which do heal under treatment, of course, are not seen by the pathologist

[13] Bogen, E Minutes of the Fourth Streptomycin Conference, Branch Office No 9, St Louis, Mo , Saturday Session, October 11, 1947, p 50

A personal communication from Dr. Siegbert Bornstein, pathologist at the U. S. Veterans Hospital, at Oteen, North Carolina, states: "Of the cases in which I have received surgical material after streptomycin treatment, I have made the following observations:

"A. I have seen a few instances of tuberculosis where the histology was in no way remarkable but after treatment with streptomycin for one or two weeks, we were unable to find acid-fast bacilli in the tissue. This, however, is in contrast to some autopsy cases where we were able to find them after prolonged treatment with streptomycin.

"B. Eosinophilia in the tissues, especially early in the treatment, is common, and is often much more pronounced than one would expect from the findings in the peripheral blood.

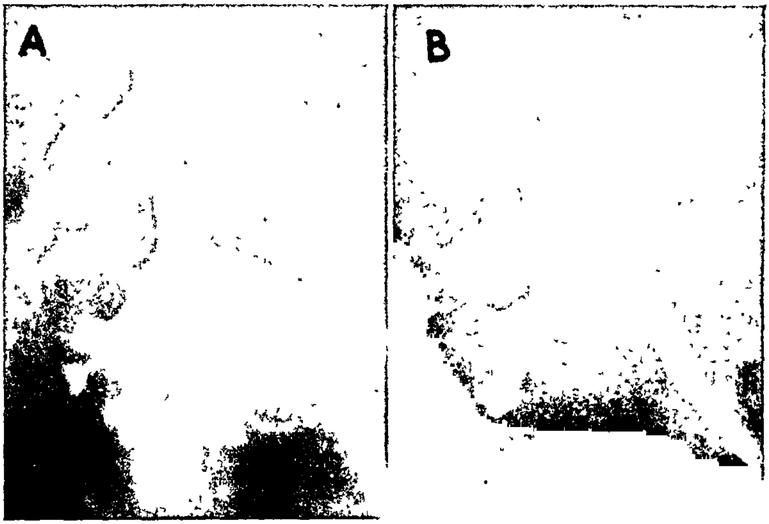

FIG. 1. *A*, typical tuberculous lesion in lower calyx, with tubercle bacilli from this kidney. *B*, healing of lesion in lower calyx after streptomycin, 60 days, urine negative.

"C. There are cases in which the impression was gained that more fibrocytes are intermixed with the epithelial cells than one would usually expect. One particular case was striking because of the peculiar presence of fibrocytes in a diffuse exudative lesion.

"D. In several cases the very large size of the Langhans cells was remarkable, but it must be said that this and the other features do not occur with any regularity."[14]

I do have 1 case, however, which I mentioned previously and will present which shows healing pyelographically (fig. 1). The patient showed a lesion in the lower calyx of the right kidney which was typical of tuberculosis. On cystoscopy the urine obtained from this kidney was positive for acid-fast bacilli, as well as that from the opposite kidney. After treatment with streptomycin the calyx became almost normal in appearance and the urine from both kidneys has remained negative for tubercle bacillus for 13 months. To date, however, I have not seen a case of renal tuberculosis with a more extensive caseo-cavernous involvement which has been affected by streptomycin therapy either in the pathological specimen or in the pyelograms. Here, perhaps, long-continued streptomycin therapy in the patient with caseo-cavernous renal tuberculosis may prove of value in preventing reinfection by a susceptible strain. I realize that this statement is readily open to attack and appears contradictory to the recent trend to shorten the course of streptomycin treatment because of the development of resistance. However, there may be the possible appearance of a sensitive reinfecting organism which has been walled off from the blood supply by the process of inspissation and, therefore, never have come in contact with the antibiotic agent. This inspissated area, which is analagous to those found in pulmonary tuberculosis with cavitation, may disintegrate with dissemination of a susceptible strain with concomitant reinfection of the kidney, ureter or bladder.

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[14] Bornstein, S.: Personal communication, March 24, 1948.

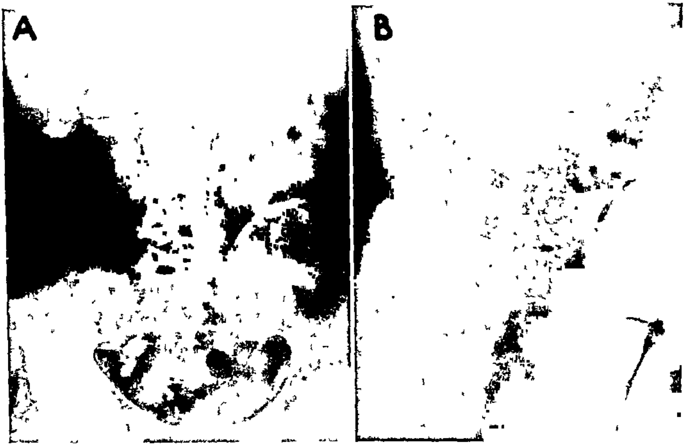

FIG. 2. *A*, calculi in right kidney and right ureter. Urine positive. *B*, ureteral calculi removed. Stones in right kidney later removed. Complete healing.

I wish to present two other cases of urinary tract tuberculosis, illustrative of the previously mentioned inoperable type of case (fig. 2).

G. C., a 68 year old white man, was admitted for treatment of chronic pulmonary tuberculosis, and draining urinary sinus, left lower quadrant, bilateral nephrolithiasis and right ureterolithiasis. The patient had previously been operated upon for left perinephric abscess, left ureterolithotomy and left orchidectomy (tuberculous). Cystograms and ureterograms confirmed the diagnosis of left ureterocutaneous fistula, positive for tubercle bacilli. Urine from the right kidney was also positive for tuberculosis. The right ureter contained 3 impacted stones and there were also 2 calculi in right renal pelvis. The blood urea nitrogen was 31 mg. Treatment consisted of streptomycin, 1 gm., 120 days, with surgery. The ureterocutaneous fistula ceased to drain on the tenth day of therapy; no acid fast bacilli demonstrated after the sixtieth day. At this time the blood urea nitrogen had increased to 49 mg. and a right ureterolithotomy was done, with removal of the 3 stones; 5 days later the blood urea nitrogen was 23 mg. On the tenth postoperative day the patient had an attack of severe substernal pain and drop in blood pressure which was diagnosed as coronary thrombosis, substantiated by the electrocardiogram. Eight months later he was in surprisingly good condition and the urine had remained negative for acid fast bacilli. Under cyclopropane anesthesia the 2 stones were removed from the right kidney and now, 4 months later, there remains a complete healing of the pyelolithotomy wound and the uretero-lithotomy wound. The blood urea nitrogen is 18 mg. See figure 3.

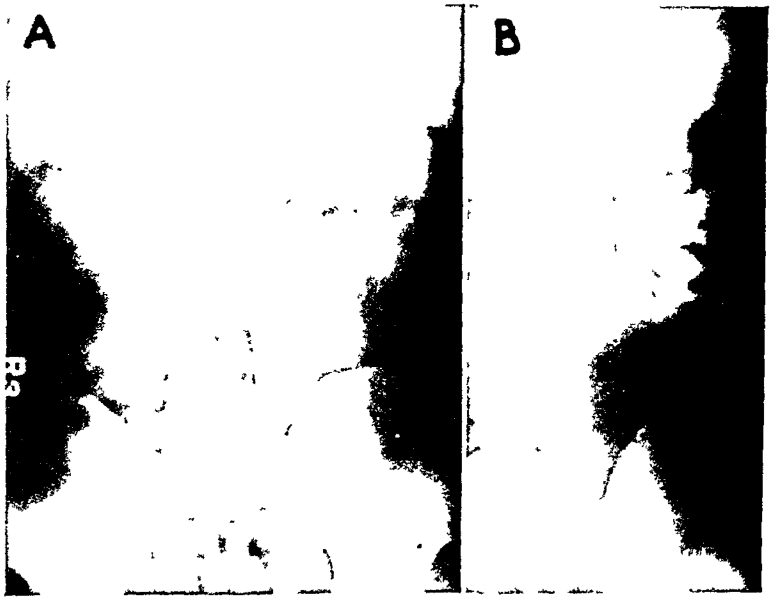

Fig. 3. *A*, tuberculous left kidney. Congenital absence of right kidney. Multiple diverticula in bladder. Left ureter inserted in prostatic urethra. *B*, permanent ureterostomy. Blood nonprotein nitrogen normal. Urine negative.

The next case was that of a younger man, L. G., 27 years old. He was admitted to U. S. Veterans Hospital, Oteen, N. C., for treatment of chronic pulmonary tuberculosis. He complained also of pain over left renal area and severe headaches. Intravenous urograms showed absent function of right kidney. At cystoscopy no right ureteral orifice was found. His left ureteral orifice was finally located in a shelving in the prostatic urethra. The urinary bladder was composed of multiple diverticula. Specimens of urine from the bladder and left kidney were positive for tubercle bacilli. The patient left the hospital but returned 5 months later because of pulmonary hemorrhage and increase in severity of headaches. The blood urea nitrogen was 31 mg., the urine was still positive, and a cavitation was noted in the left apex. The kidney pelvis, calyces and left ureter had become greatly dilated, with a severe kink in upper left ureter. The total phenolsulphonphthalein output for 2 hours was 25 per cent. The blood urea nitrogen was elevated to 52 mg. Five days later a uretorostomy was done above the kink and streptomycin therapy started. One week later the blood urea nitrogen was reduced to 22 mg., the headaches had ceased. One year later the ureterostomy tube is still in, but the wound has been healed since the second week and the urine from the ureterostomy tube is negative. There has been no urine from the bladder, substantiating the original diagnosis of functionless right kidney. Never before have I seen complete, first intention wound healing in cases where it was necessary to open the tubeculous urinary tract and establish drainage. Apparently streptomycin has made this possible. See figure 4.

One of the most undesirable complications of genital tuberculosis has been eliminated through the combination of streptomycin and surgery on scrotal sinus tracts. We no longer hesitate to incise a tuberculous abscess in this region and establish drainage, since with the immediate institution of streptomycin, rapid healing is the rule. Later epididymectomy can be done, and in all our cases, must be done, since no such case permanently heals.

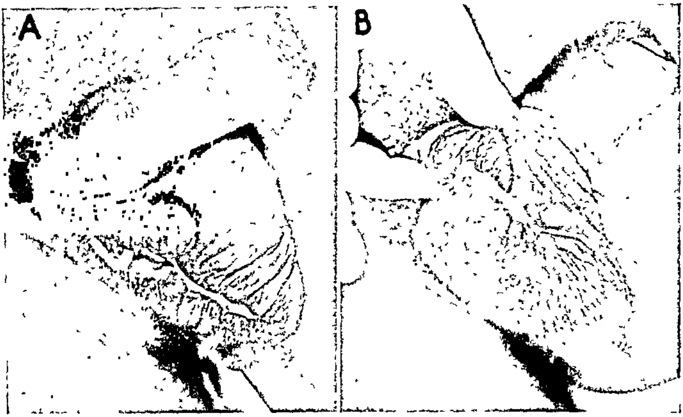

Fig. 4. *A*, no streptomycin. *B*, after 8 days' streptomycin, showing rapid healing and closure of sinus.

The efficacy of two daily doses or intermittent therapy on the tubercle bacillus may not seem consistent with the idea of a predominantly bacteriostatic effect. By contrast, penicillin is known to have a bactericidal as well as a bacteriostatic effect, and today we strive to devise methods of obtaining a more prolonged effect from each dose assuming that continuous action is more physiological than intermittent action. Evidence clinically and experimentally shows that this principle of penicillin therapy is not applicable to streptomycin. Why this is not so has yet to be clarified. We may expect, therefore, that further changes in dosage and in the interval between doses, will have to be made, and cannot regard the present method of administration as the final one.

CONCLUSION

In our experience with streptomycin therapy in 59 cases of genito-urinary tuberculosis, we have been able to bring about at least temporary arrest of the process with obvious immediate benefit in 82 per cent of our patients. In those in which we have noted no definite change as a result of this therapy, we have at least noted a palliative effect. We have observed that the appearance of the cannulized tracts, notably the ureters, has paralleled that of ulcerative lesions of the air passages which regularly respond well to streptomycin therapy. See tables 1, 2, 3, 4, 5.

TABLE 1. *Protocol 1, 2 gm./day. Diagnosis made on pyelographic studies, cultures, guinea pig studies*

CASES 7	DURATION OF RX	NO. OF PTS. WITH NEG. CULTURES AT END OF						FAILURES	DEATHS
		2 mos.	4 mos.	6 mos.	9 mos.	12 mos.	18 mos.		
	days								
3*	120	1				1		1†	2‡
4	120	4	4	4	4	3	2	2	0

* One patient expired at 30 days, st. asthma.
† One patient negative for 13 mos. Now pos. bilateral.
‡ Necropsy failed to reveal any healing of renal disease after 5 mos.

TABLE 2. *Protocol 1, 1 gm./day (0.5 gm. b. i. d.). Diagnosis made on pyelographic studies cultures, guinea pig studies*

CASES 11	DURATION OF RX	NO. OF PTS. WITH NEG. CULTURES AT END OF						FAILURES	DEATHS
		2 mos.	4 mos.	6 mos.	9 mos.	12 mos.	18 mos.		
	days								
2	More than 120	2	2	2	2	1	1	1	0
	120								
6	120	5	5	5	5	5	1	2	0
1	110	1	1	1	1	1	1	0	0
1	90	1	1	1	1	1	1	0	0
1	Less than 90	1	1	1	1	1	1	0	0

As in the illustrative cases, we have been able to perform surgical procedures with the aid of streptomycin in patients who would have been abandoned surgically because of the complications which would have been certain to arise and for which we would have no remedy without streptomycin.

Though the last word on chemotherapy of tuberculosis has not been said, much has already been done and research in some of the newer antibiotics has been very promising. The human body can kill the tubercle bacillus if given enough time. Perhaps the desired answer will be in the form of a drug which merely

TABLE 3. *Protocol 2, 1 gm./day (0.5 gm. b. i. d.), cystitis*

CASES	DURATION OF RX	NO. OF PTS. WITH NEG. CULTURES AT END OF						FAILURES	DEATHS
		2 mos.	4 mos.	6 mos.	9 mos.	12 mos.	18 mos.		
	days								
3	2–120 1– 60 Nephr. '45 TBC		2	1				0	0

CASES	BLADDER CAPACITY CHANGES		IMPROVEMENT IN BLADDER SYMPTOMATOLOGY DURING RX (WEEKS)							
	Pre	Post	2nd	4th	6th	8th	10th	12th	16th	None
	cc.	*cc.*								
3	1–40 1–60 1–75	400 350 425	2		1					

TABLE 4. *Genital tuberculosis, 1 gm./day (0.5 gm. b. i. d.)*

	CASES 38	DAYS OF RX	RESULTS		FAILURES	REMARKS
			Drainage ceased	Healed		
			days	*days*		
Sinuses P. O. 4 mos. to 5 yrs.	12 5	120	9	15	0	
Erupted and drained	3 3	120	10	23	0	
Preop. strept. (1 wk.) plus surgery	3 5	120	0	8	0	
Prostatorectal sinus	1	120	10	21	0	
Ureterocutaneous fistula	1 2	120	10	20 26	0	
Developed during treatment	1	erupted and drained 4 mos. (1000 microg, res.)			1	
	2 developed without drainage, unimproved.				2	Expired meningitis

TABLE 5

	NUMBER OF PATIENTS	CYSTOSCOPIC IMPROVEMENT	SYMPTOMATIC IMPROVEMENT	STERILE URINE	UNCHANGED	WORSE	DEAD
R..........	21	54%	82%	62%	5%	2.5%	9.5%
G..........	38	0	0	0	2.6%	0	.5%

holds in check the tuberculous process while the human body destroys the organisms themselves.

At a recent meeting of the Streptomycin Committee, in Chicago,[15] it was noted that the tubercle bacillus tends to show resistance to streptomycin on the forty-fifth day of therapy. With this in mind, it was decided to reduce the duration of the period of streptomycin treatment to 42 days instead of 120 days, the length of time formerly recommended. When a patient is improving and no toxic symptoms of the drug are evident, the physician is often reluctant to discontinue treatment by the forty-second day. But at this point he should carefully weigh the resistance factor against what improvement might be gained beyond this date. This immediately poses the question, does streptomycin act as a booster to the patient's immunity after reducing the bacillary census?

I should like to add here that the only acceptable statistics today (based on a very large number of cases) are those of the Veterans Administration. For several years the Veterans Administration has followed a rigid protocol and it is only by such fine adherence to this protocol, modified from time to time, that any worthwhile data can be compiled. To warrant safety in the general use of streptomycin, the urologist must acquaint himself with dosage, permanence of resistance and reactions to the drug. The patient must be under constant observation and certain minimal laboratory procedures carried out.

The factors, interpretations and conclusions drawn from the experience of treating 59 cases of genito-urinary tuberculosis with streptomycin have been presented.

409 Flatiron Bldg., Asheville, N. C.

[15] Moyer, R. E.: Personal communication, April 18, 1948.

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DISCUSSION

Dr. Leon Herman (Philadelphia, Pa.): The biochemistry of streptomycin, the reaction to it of certain strains of bacilli—its activity—the dosage, its toxicity, and so on have been adequately discussed and need no further consideration.

Dr. Huffines holds that this agent is incapable of eradicating the tubercle bacillus from the human body, and that arrest of tuberculosis in man is its maximum potential effect. This opinion has a reasonable basis in clinical experience, notwithstanding the established fact that the drug is lethal to many strains of tubercle bacilli if brought into direct contact with them in proper concentration.

Furthermore, streptomycin is admittedly destructive of minimal or early lesions in the lungs and elsewhere so that therapeutic failure must often be attributed to inacessibility of the bacteria in sclerotic lesions rather than to inherent impotence of the drug.

The fact is that the majority of tuberculous lesions encountered by the surgeon are of long standing, and for this reason it is proper and necessary to employ streptomycin as an adjuvant in treatment, but that this will prove eventually to be its sole function should not be conceded as yet.

Dr. Huffines attempts to illustrate the effect of streptomycin on early and late lesions of the kidney with the recital of 3 cases in which tubercle bacilluria from an otherwise apparently normal kidney was eradicated by streptomycin therapy before surgical removal of the obviously diseased kidney on the opposite side.

I wish we could accept this evidence without question, but the probabilities of obtaining contaminated specimens from the healthy kidney are such that one hesitates to accept this as evidence of cure by streptomycin therapy, or to use it in support of Medlar's therapy. However, I heartily agree that streptomycin given before or after nephrectomy may minimize the danger of tuberculosis of the remaining kidney, whatever its pathogenesis. Urologists generally are unwilling to substitute streptomycin therapy for nephrectomy in operable cases. This soon became evident in answers to a questionnaire; we found no one who had used, or expressed a willingness to use streptomycin in a case of unilateral renal tuberculosis. And now Dr. Huffines reports such a case with most satisfactory results. The event is so rare that I would like to describe a similar case.

A young married woman developed tuberculosis in girlhood. Later she had tuberculosis of the right shoulder joint, and 3 years before coming to us, a spinal fusion was done. Urinary tract symptoms appeared in May 1947. Tuberculosis lesions in the form of conglomerate tubercles in the pre-ulcerative stage surrounded the orifice of the right ureter. The urine from the right kidney contained tubercle bacilli while that from the left kidney was sterile.

This slide shows typical tuberculous lesions involving the superior major calyx of the involved kidney. The patient was given 78 gm. streptomycin and by October the urine was sterile and pus free, and it has remained so.

This next slide shows a pyelogram made in October, and I think there is evidence that the lesion is healing. The next slide is that of a pyelogram made in April 1948 and demonstrates complete disappearance of the lesion. The bladder lesions have disappeared and the patient is clinically well. During the course of treatment the patient developed severe pain referable to the involved kidney and she also had gross hematuria.

Dr. Huffines' results in the treatment of tuberculous sinuses are somewhat better than our own and in this connection it may be of interest to remark that one of our patients, while undergoing streptomycin therapy, developed subacute tuberculous epididymitis necessitating orchidectomy.

In conclusion may I say that the data to which much has been added today, will, when complete, enable us to evaluate streptomycin therapy in urogenital tuberculosis far more scientifically than is possible at the moment.

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THE TREATMENT OF GENITO-URINARY TUBERCULOSIS WITH STREPTOMYCIN ALONE.[1, 2, 3]

JOHN K. LATTIMER, J. BURNS AMBERSON AND STANLEY BRAHAM
From the Veterans Administration Hospital, Bronx, N. Y.

Two hundred and fifty-three cases of genito-urinary tuberculosis have now been treated with streptomycin by the Veterans Administration, Army and Navy Research Group. As a result of this experience, a few generalizations can now be made concerning the questions of optimum dosage and limitations of the drug.

METHODS

Patients with all types and all stages of tuberculosis were treated. Twenty-one of the first 25 patients treated had additional tuberculous lesions outside the genito-urinary tract. Positive cultures or guinea pigs from the urine were the criteria required for a diagnosis of genito-urinary tuberculosis. Nine consecutive 24 hour urine specimens were cultured every month during the treatment. All patients have been followed for more than 12 months and the urines have been cultured every 3 months during this period. Cystoscopic examinations were made and the findings drawn graphically on a chart, each time, for comparison. Ureteral cultures were taken at each cystoscopy. Cultures of the bladder urine were made for secondary organisms and a careful count of the pus cells in aliquots of each ureteral specimen was made. The bladder capacity was measured at each cystoscopy. A routine urinalysis was done every 2 weeks as were determinations of blood urea nitrogen, erythrocyte sedimentation rate, phenolsulphonthalein test, urine concentration test, blood count, total serum protein, albumin and globulin determination. Regtrograde pyelograms were done before and after treatment and every 6 months subsequently. Urine cultures were grown first on Petrik's medium and then sub-cultured on Dubos liquid medium for pure culture streptomycin sensitivity tests. The sensitivities of all cultures were determined. Audiograms and caloric tests were done every 2 weeks on every patient. A careful chart was kept of the frequency of urination, pain on urination and all other symptoms and toxic manifestations.

CRITERIA OF IMPROVEMENT

There are several possible criteria of improvement in renal tuberculosis: 1) the disappearance of the tubercle bacilli from the urine; 2) the arrest of the

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[1] Read at annual meeting, American Urological Association, Los Angeles, Calif., May 17, 1949.

[2] This study is one part of a co-ordinated large scale program of investigation into the effects of streptomycin on tuberculosis of all types, now being conducted by the Veterans Administration, the Army and Navy. Since their veteran patients will be followed indefinitely by the Veterans Hospitals, they present an unparalleled opportunity for long term follow-up.

[3] Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

destructive process; 3), loosening of strictures; 4) fibrosis and/or calcification; 5) clinical improvement of symptoms; and 6) the disappearance of pyuria. The most demanding criterion is the disappearance of tubercle bacilli from the urine, and this study is, therefore, presented in terms of the per cent of cases successfully converted from positive to negative for tubercle bacilli in the urine. This may be too rigorous a criterion. Perhaps we should be content if the destructive lesions stop progressing or if symptoms improve, even though the urine remains positive for tubercle bacilli. Symptoms improved and pyelographic changes remained static much more frequently than did the tubercle bacilli disappear from the urine, in this series.

It has been suggested that the increased fibrosis, hastened by streptomycin, is a sign of healing. Unfortunately this rapid fibrosis may have disastrous effects on badly infected ureters, causing them to contract and become occluded. If such a ureter serves a solitary kidney, a nephrostomy must be done. We have seen this happen in 2 out of 50 cases with renal tuberculosis. It has also been suggested that calcification is a sign of healing, but 6 of the 7 renal lesions in this group which contained calcium failed to be converted to negative. It was noted that even when the tubercle bacilli disappeared from the urine, pyuria continued in most of the cases.

DOSAGE

Several dosage regimens were compared. It was found that the greatest percentage of conversions from positive urine to negative was seen among the patients who received the largest amount of the drug, and for the longest period of time (fig. 1). The best bacteriological results were obtained in a group of 64 patients who received 2 gm. of streptomycin daily for 120 days, in divided doses every 4 hours, day and night. The urine was initially converted from positive for tubercle bacilli to negative in 81 per cent of these cases. After 1 year the percentage had declined only 19 per cent, so that 62 per cent still had negative urines after 12 months. There is some indication that with the elapse of more years of follow-up this percentage of successful conversions will decline even farther. It must be remembered, however, that in the days before streptomycin, 62 per cent conversions of the urine for a period of 1 year was unheard of.

A second group of 42 patients was treated with 1 gm. streptomycin for 120 days; the drug being given as 0.5 gm. every 12 hours. This regimen was found to be much less toxic but the results were not so good as with the 2 gm. for 120 days. There were 58 per cent initial conversions but only 46 per cent of the original group remained negative for tubercle bacilli in the urine longer than 6 months. It is to be expected that there will be a further decrease in the number of successes as time goes on. The third group of 103 patients was treated with 1 gm. streptomycin daily for only 42 days, given in 2 doses of 0.5 gm. every 12 hours. In this group there were 50 per cent immediate conversions to negative but among those who were followed for a 6 months' period it was found that the total percentage of conversions had fallen practically to zero. When the dose was cut down even further in a fourth group of 39 patients, to 0.5 gm. for 42 days, the results were entirely unsatisfactory. As might be expected, there was no toxicity in these latter two groups who received smaller doses.

A more detailed analysis of these data is still to be made. The size and activity of all the lesions treated must be reviewed before really good comparisons can be made between regimens which differ as little as do the 2 gm. 120 days (62 per cent successes) and the 1 gm. 120 days (46 per cent successes). This further review must await the analysis of individual case report forms which are now being prepared. It has been suggested that 0.5 gm. every 12 hours for 90 days may give a fair degree of benefit for a minimum of toxicity. It seems logical however, that toxicity should be ignored and the most effective long course be given, in view of the lethal nature of renal tuberculosis.

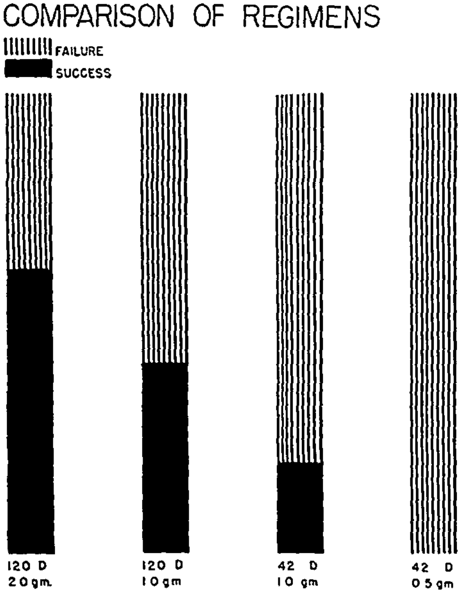

FIG. 1. Tubercle bacilli were eliminated from urine most successfully by the 2 gm., 120 day streptomycin treatment regimen (left column). As dosage was reduced or treatment shortened, results became proportionately poorer (right).

LIMITATIONS OF STREPTOMYCIN

A detailed correlation between the effectiveness of streptomycin treatment and the volume, activity and type of pathology in the kidneys, was made in 25 pilot cases. Any patient who has tuberculosis in one kidney must be presumed to have dormant but potentially active tubercles in the other kidney.

Pathogenetically, genito-urinary tuberculosis is usually hematogenous from a tuberculous pulmonary lesion. Medlar estimates that 25 per cent of pulmonary tuberculosis patients develop tubercles in both kidneys. Most of these heal, but from 3 to 5 per cent of the total go on to ulcerating, progressive, destructive renal tuberculosis. Of the 6,000 patients with all types of tuberculosis who have been treated by the Veterans Administration in this research project, the 253 genito-urinary cases represent about 4 per cent of the total. This incidence of urinary tuberculosis is in accord with the figures reported from other series. Other hematogenous lesions are of course very common in patients with genito-urinary tuberculosis. Eighty per cent of our first patients with urinary tuberculosis had tuberculous foci elsewhere in the body. In some cases the pulmonary focus heals, leaving the genito-urinary lesion as the only active tuberculous focus in the body.

In the patients who do develop active, destructive, renal tuberculosis, the activity usually starts in one of two ways.

1. The small dormant parenchymal tubercles may break down and follow a tubule down to the surface of a papilla. Here an ulceration occurs on the surface of the pelvis. Tubercle bacilli and pus may then appear in the urine, with or without symptoms. The ulcer is now superficial and will cause no irregularity in the pyelogram. Such lesions at first contain little necrotic tissue and probably respond well to chemotherapy.

2. Another course which the parenchymal tubercles may follow is to cause extensive local caseation in an adjacent area of the parenchyma. This may later liquefy and slough into the pelvis leaving a large cortical abscess cavity. This appears in the x-ray as an "extra calyx". These lesions are accompanied by so much necrotic and fibrous tissue as to have a dubious prognosis.

Progression of the lesions which reach the renal pelvic lining is in the direction of a gradual spreading of the areas covered by tuberculous granulations. These chronic ulcerations are accompanied by dense layers of fibrous and caseous diseased tissue. The involved calyces may appear clubbed, moth eaten, or narrowed to the point of being pinched off at the infundibula.

The latter lesions respond poorly to streptomycin partly because the layer of thick, necrotic, fibrous tissue surrounding them is so dense that the drug probably cannot penetrate it to reach the tubercle bacilli growing in the necrotic tissue (fig. 2). Leukocytes are also unable to penetrate the fibrous coat to destroy the tubercle bacilli after they are affected by the drug. As the lesions grow larger, they may spread to other calyces. They destroy the renal parenchyma and may partially calcify.

Strictures of the minor and even major calyces now form, causing hydronephrosis and complete atrophy of portions of the kidney. Finally the pelvis and ureter may become strictured with complete destruction of the functioning kidney tissue. Any kidney lesion which contains fibrous or necrotic tissue, even in small amounts, will probably be refractory to streptomycin treatment. It may also be presumed that any of these necrotic lesions which are present will deform the pyelogram. Even a slight deformity of the pyelogram probably implies the presence of enough fibrous tissue to make the prognosis for medical treatment very poor. On the other hand, if the lesion can be detected while it is still so small that it does not deform the pyelogram but is discharging tubercle bacilli and pus into the urine, the lesion may be amenable to chemotherapeutic treatment. It must be realized, of course, that even though the pyelogram is not deformed, there may still be large areas of cortical necrosis elsewhere in the kidney. It can only be hoped that the action of the streptomycin will heal over the surface ulcerations and slow down the tendency to liquefaction of such large caseous foci, permitting fibrosis and healing to occur. The development of resistance of the organisms to streptomycin is another limitation which is discussed below.

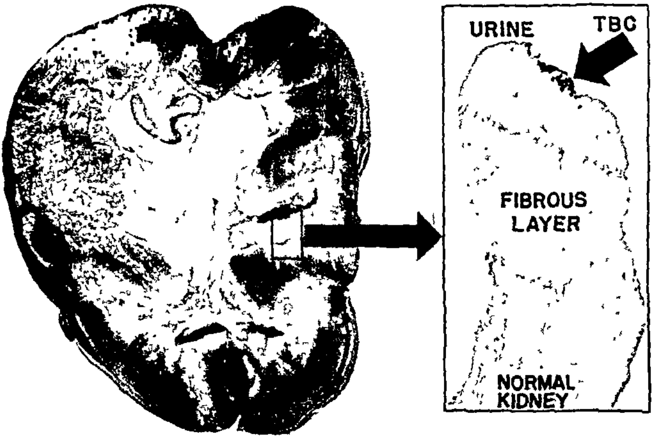

FIG 2. Black dots (arrow) were colonies of tubercle bacilli growing in free margin of thick, avascular, fibrous lining of tuberculous calyx Note their distance from blood supply and their nearness to streptomycin-laden urine.

ADVANCED RENAL LESIONS: RESULTS

The definition of an advanced renal lesion was therefore arbitrarily taken as "any lesion large enough to be definitely visible in the pyelogram." This even included cases where only a single calyx was involved. When a lesion had gone far enough to show in the x-ray, it seemed probable that it was already surrounded by an area of fibrous and necrotic tissue. Unfortunately, large renal lesions of this type constitute the largest and most important group of patients from the viewpoint of the urologist. Most patients with renal tuberculosis are not discovered until they are in this advanced stage, which is the most difficult to check. Streptomycin alone, in the 2 gm., 120 day series, checked only about 25 per cent of our cases which fell into this classification (fig. 3). Many additional cases became negative for a period of from 3 to 6 months but then again became positive. It is probable that the surface ulcerations of these large lesions were temporarily healed over and that the number of tubercle bacilli in the urine was reduced for the time being, but as time went on new ulcerations appeared in the pelvis and tubercle bacilli again appeared in the urine. It was noted, however, that those who did remain positive and those who reverted to positive, ran a more benign course than might otherwise have been expected had they not been treated with streptomycin. Symptoms and urinary sediment were certinly improved in most of the patients, even when the urine remained positive.

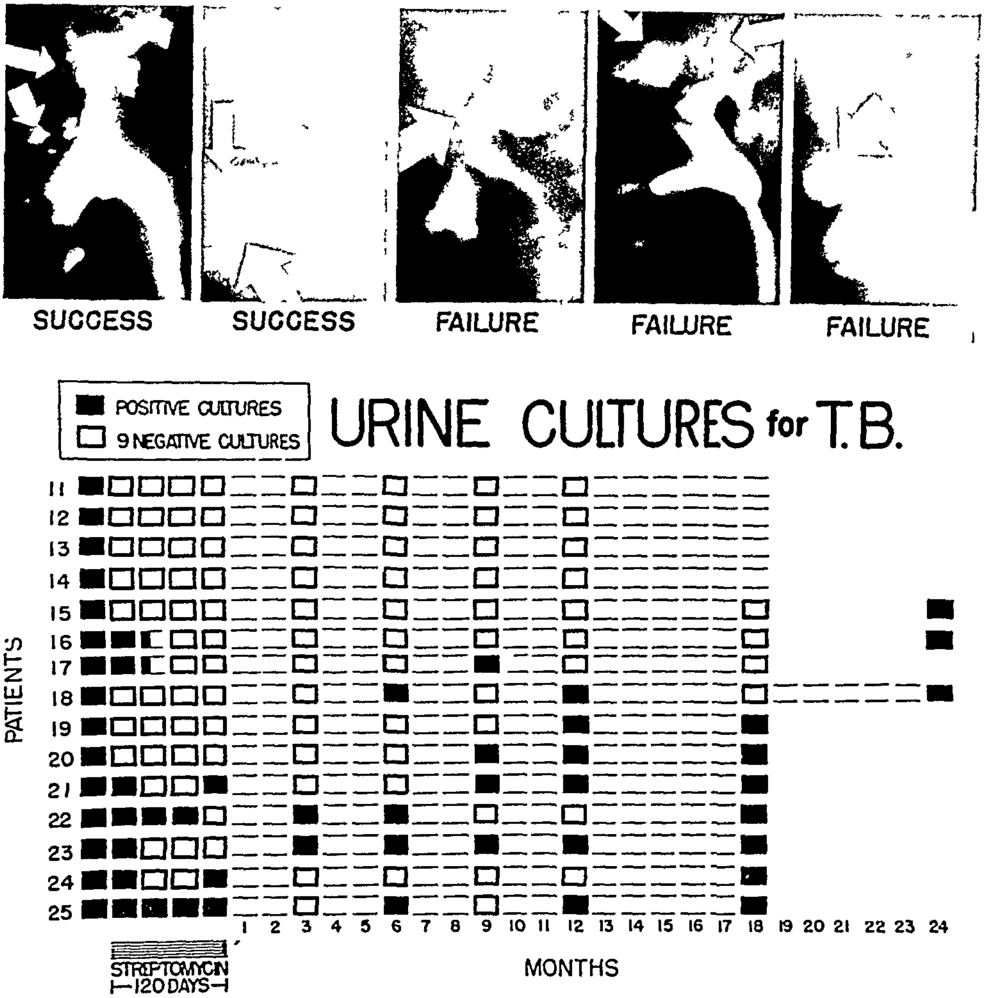

FIG. 3. Large renal lesions like these were clearly visible by x-ray. Tubercle bacilli were successfully eliminated from urine in only 25 per cent of such cases. Many cases became positive again after several months. (See bacteriology chart below x-rays.)

SMALL RENAL LESIONS: RESULTS

Kidneys with small renal lesions responded well to treatment with streptomycin. A small renal lesion was arbitrarily defined as "one which was giving off tubercle bacilli and leukocytes into the ureteral urine but which was too small to cause distortion of the pyelogram." This was a precarious method for classifying renal tuberculous lesions on the basis of shadows which they cast, or did not cast, on an x-ray film, but it was the only clinical method available to us at that time (fig. 4). Of the pathology, it could only be said that it was not sufficiently extensive to cause distortion of the pyelogram. Errors in such a classification are of course easily made but it has been our observation in this group of patients that even areas of necrosis which were about to slough were heralded by amputated calyces or constricted calyces in adjacent areas. The technique of pyelography became especially important in classifying these cases. Gentle retrograde pyelograms with multiple exposures in different rotations were necessary to detect some of the lesions. Intravenous pyelograms were often necessary in order to fill cortical cavities whose infundibula would not admit the retrograde dye. In one pilot series 8 out of 10 such kidneys became negative, and the remaining 2 are probably negative (fig. 5). Unfortunately, patients with small renal lesions are almost never seen by the practicing urologist. They may be found by the urologist who removes a tuberculous kidney and then watches the other "good" kidney for the first sign of breakdown in the form of white blood cells or tubercle bacilli. They may be also found by the medical man who specializes in pulmonary tuberculosis who watches his patients for pus cells, albumin or tubercle bacilli in the urine as part of the routine checkup. A periodic urinalysis should certainly be done on every patient who has tuberculosis in any part of the body.

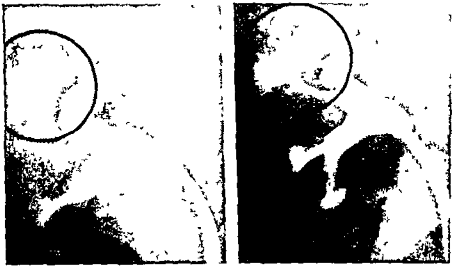

FIG. 4. Large cortical cavities with narrow openings are easily missed (left). Repeated careful pyelogram finally disclosed large area which had sloughed out (right).

TUBERCULOSIS OF THE URETER

Narrowing of the ureter was seen in a few cases. In one instance where the narrowing was so severe that it caused shortening of the ureter, the treatment with streptomycin appeared to hasten the fibrosis, with further shortening and constriction of the ureter, resulting in the complete obliteration of the tube. Caution must be exercised in the treatment of solitary kidneys with severe ureteritis. In other cases where the obstruction appeared to be the result of superficial ulcerations or edema without shortening or fibrosis of the ureter, the action of streptomycin was distinctly beneficial. It caused the stricture to loosen and the hydronephrosis and hydroureter to disappear as treatment progressed (fig. 6). Here again superficial lesions appeared to improve while advanced lesions were not benefited.

TUBERCULOUS CYSTITIS

Superficial bladder ulcerations healed rapidly under streptomycin treatment. They were greatly improved in 4 weeks and in many cases completely gone at the end of 8 weeks. Symptoms improved rapidly as the areas of superficial cystitis receded. Patients who had had extreme frequency and urgency were able to get more sleep with the lengthened period between voidings. As a result, the patients who were debilitated regained their weight. These findings were supported by biopsies from superficial ulcerations which showed the disappearance of leukocytic, epithelioid, and round cell infiltration after the ulcerations healed. Residual cystitis after nephrectomy, or cystitis secondary to the overflow of organisms from a tuberculous prostate, was treated with streptomycin until the cystitis was gone, so as to prevent contractures of the bladder. Patients whose bladders showed superficial acute lesions, with capacities of only 300 cc, frequently saw their capacities increase to 500 cc by the end of treatment. It was

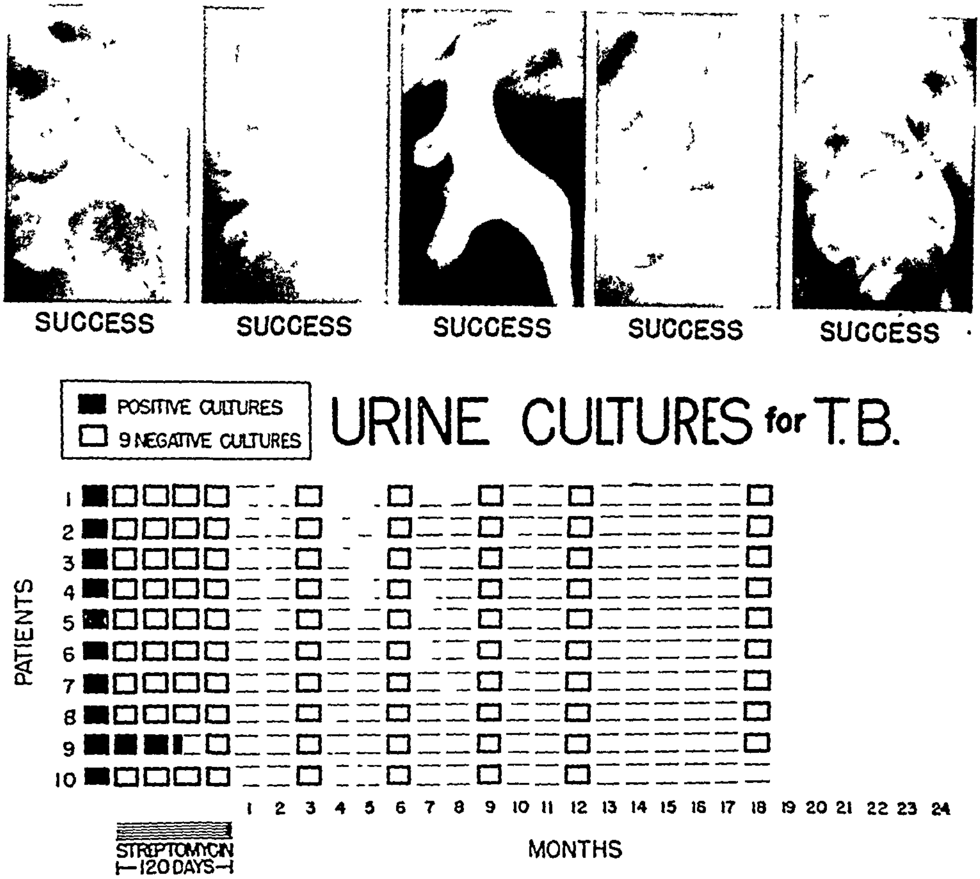

FIG. 5. These kidneys had small active renal lesions with tubercle bacilli and pus in the ureteral urine. Lesions were too small to show by x-ray. Tubercle bacilli were successfully eliminated from urine of from 80 per cent to 100 per cent of such kidneys. (See bacteriology chart below x-rays.)

noted that the bladder lesions recurred if the kidneys broke down and again became positive for tubercle bacilli. It was also our impression that cystitis cleared more rapidly when the drug was given around the clock in doses every 4 hours, rather than in doses every 12 hours. It is reasonable that a urinary level which is maintained throughout the 24 hours might conceivably have a greater beneficial topical effect upon the bladder lesions than that from intermittent therapy.

Deep seated fibrous contractures of the bladder were not helped by streptomycin; where fibrosis of the bladder was present before treatment, it was still present after treatment. Bladder capacities which averaged 50 cc before treatment, improved very slightly to about 100 cc but never improved significantly.

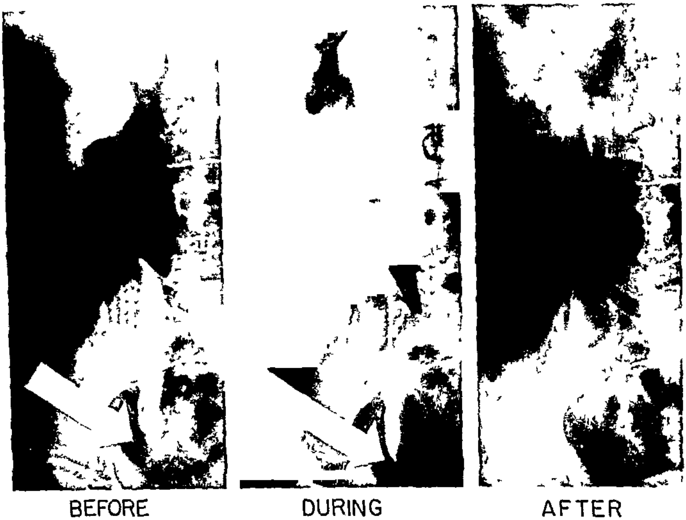

FIG 6 This mild ureteral stricture loosened up after streptomycin treatment Other more advanced cases stenosed rapidly after streptomycin treatment

PROSTATIC TUBERCULOSIS

Prostatic tuberculosis did not appear to be greatly benefited by streptomycin treatment (fig. 7). This was probably related to the nature of the pathology of prostatic tuberculosis. Palpable prostatic lesions occurred in 20 of the first 25 patients They usually occurred as elongated cords located in the lateral lobes of the prostate gland. These nodules were usually well encapsulated masses of soft caseous material. The diagnosis was supported in all but one of the cases by the finding of dilated "golf hole" prostatic ducts. Dilated ducts were found in 5 more who had no palpable pathological change. It was apparent that it was often impossible to tell a tuberculous prostate from a normal or small prostate.

Prostatic smears were not generally taken for fear of disseminating the tuberculosis. Examination of the semen for tubercle bacilli produced only 1 positive out of the 15 made. No cases of genital tuberculosis were reported among the 15 wives of 12 patients with prostatic or epididymal tuberculosis. Most of the nodules remained essentially unchanged both during and subsequent to treatment. In a few cases there was a slight decrease in size but none of the nodules disappeared. Some new nodules appeared even during treatment. There was perhaps a general trend toward slight improvement.

Superficial ulcerations sometimes occurred on the surface of the posterior urethra and the adjacent bladder floor due to irritating tuberculous material from the prostatic ducts. The urine would then become positive for tubercle bacilli. These superficial urethral and bladder lesions all responded well to streptomycin. The urines of these cases all became negative as symptoms and redness diminished.

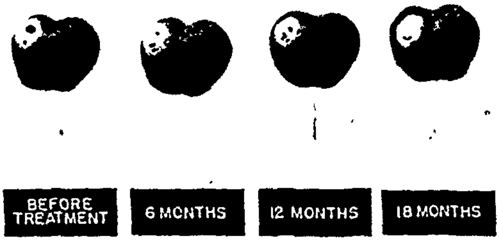

FIG. 7. Prostatic nodules usually did not improve with or after streptomycin treatment.

It is our present policy to defer treatment for tuberculous nodules in the prostate which are causing no trouble. If ulceration in the posterior urethra and onto the bladder surface occurs, with severe symptoms and the possibility of a bladder contracture, streptomycin is given and kept up until the symptoms are controlled or resistance to the drug develops.

TUBERCULOUS EPIDIDYMITIS

Tuberculous epididymitis usually did not respond well to streptomycin. The pathology of tuberculous epididymitis is one of massive necrotic caseous foci surrounded by fibrous tissue. The infection may be either hematogenous or descending via the vas deferens from the prostate. The onset may be insidious with the slow formation of a nodule in the epididymis, or it may be very acute with diffuse swelling resembling gonorrheal epididymitis. If the swelling persists for several weeks despite penicillin and sulfa treatment, tuberculosis can be suspected. Thickening of the vas deferens was not a constant feature in our patients. When it was present, it made the diagnosis even more likely, but in the purely hematogenous cases it was sometimes absent. Tuberculous nodules in the epididymis usually blocked the lumen, but not always. For instance, one of our men had a sperm count of 79 million per cubic centimeter in spite of the fact that he had large nodules in both epididymides There were 13 epididymal nodules in the first 25 patients Twelve of these remained unchanged after streptomycin treatment and one acute epididymis improved slightly A few of these nodules were removed after 18 months and were found to still contain soft caseous centers even though tubercle bacilli were not recovered from them Two cases of acute tuberculous epididymitis did not shrink down any more rapidly than usual when streptomycin treatment was given Draining tuberculous sinuses showed a slight diminution in the amount of drainage but continued to drain until the necrotic epididymis was removed Patients who had a superficial residual draining sinus at the site of a postoperative epididymectomy or nephrectomy healed up quickly after 3 weeks of streptomycin Here the sinus tract was apparently not yet accompanied by a fibrous or necrotic area and chemotherapy was effective

STREPTOMYCIN AND SURGERY

Excision appeared preferable to streptomycin treatment for any lesion where there was a large amount of necrotic tissue In cases with unilateral active, progressive tuberculosis of the kidney, the kidney is now excised as soon as it has been determined that the remaining kidney shows no activity in the form of tubercle bacilli or pus in the urine Excision is also the treatment of choice for active tuberculous epididymitis Both nephrectomy and epididymectomy are accompanied by a short course of streptomycin It is our practice to give 0 5 gm streptomycin every 12 hours for a period of 3 weeks following any operation on a tuberculous organ This dosage is still experimental but we start the treatment 2 or 3 days before operation and continue it for the balance of the 3 weeks after operation We do not exceed 3 weeks of treatment because resistance to streptomycin is more prone to develop after 3 weeks Pending the development of additional tuberculostatic drugs, we believe that it is extremely important not to squander 120 days of streptomycin upon inactive foci which may not respond It is important not to make the patient's organisms resistant by administering 120 days of streptomycin after the active foci have been excised The 3 weeks' course is aimed at the possible prevention of hematogenous dissemination It is our experience that this course of medication does not protect the patient against a wound infection at the site of operation, if tubercle bacilli are spilled in the wound in any quantity Because of this fact it is our practice to leave the ureter or the vas deferens intact until the wound is entirely closed The tube is then clamped and cut outside the closed incision After 5 days the stump is permitted to drain onto the skin until it withers and dries up It has not yet been determined whether or not 3 weeks of streptomycin is sufficient to do any good at all in advancing the healing of the dormant tubercles which we presume to be present in the remaining good kidney It seems to us to be unwise, however, to give a longer course at this time, aimed at inactive lesions, since it would make the organisms resistant and thus have squandered the patient's only therapeutic weapon, should he later develop the meningitis or renal tuberculosis which kills so many of these people

TOXICITY

On the 2 gm., 120 day regimen, all of the 25 pilot patients developed some permanent loss of vestibular function as measured by caloric tests. Some of the patients were markedly dizzy and some patients were not dizzy at all. All of the patients showed a permanent vestibular loss which came on after about 30 days of treatment. After treatment was stopped, the patient's dizziness began to improve and with the addition of eye exercises and co-ordination exercises, the ataxia has been compensated for by almost everyone. The corrective exercises employed were designed to improve the efficiency of the visual and muscle, joint and tendon senses in maintaining equilibrium. Most of these men have compensated for the vestibular loss so well that they are not handicapped. Hearing loss was not a prominent feature on this regimen. Rises in blood urea nitrogen were not severe, although in some cases there was a slight transitory rise to about 40. Since many of these patients had only one fragment of a solitary kidney remaining and since their kidney function did not suffer, it was concluded that this dosage was not markedly toxic for the kidney. In a few patients, skin rashes became severe and in 2 of 24 cases, compelled curtailment of the treatment. When the dosage was reduced to 1 gm. for 120 days, toxicity was markedly reduced but so was the effectiveness of the drug against the tubercle bacilli. Intermittent and repeat courses of streptomycin were less toxic than continuous treatment.

RESISTANCE

Tubercle bacilli from all these patients were sensitive to streptomycin at the beginning of treatment. In those cases which continued to show tubercle bacilli in the urine in spite of treatment, there was a marked rise in resistance as time went on. It should be recorded here, however, that even after test tube resistance had developed, symptoms were sometimes improved by repeated additional courses of streptomycin.

NEW TREATMENT REGIMEN

During the coming year, a combination of streptomycin and para-aminosalicylic acid (PAS) will be investigated. PAS is an additional tuberculostatic agent whose action is similar to that of a sulfa drug. It has been widely used in Sweden and Europe against tuberculosis. The results there are said to be of the same magnitude as those reported with streptomycin in this country although the results were not achieved as rapidly as with streptomycin. There is some evidence that PAS may be effective against those strains of tubercle bacilli which are resistant to streptomycin. There is also some indication that when the two drugs are used in combination, there may be a delay in the development of resistance to streptomycin and the therapeutic effect may be enhanced. It is hoped that the combination of the two drugs will make it possible to reduce the dose of streptomycin to a non-toxic level. With large renal lesions it may be necessary to keep up the PAS (12 gm. daily) for as long as 6 to 12 months. The nausea and diarrhea sometimes caused by the PAS must be more satisfactorily dealt with before it can be freely used for debilitated patients.

SUMMARY

Pathogenesis. When active tuberculosis is found in one kidney, it must be suspected that there are dormant tubercles in the other kidney which may later become active if resistance is lowered. Active tuberculosis destroys the kidneys primarily by the formation of strictures. Ulceration and cavitation tend to perpetuate the disease.

Dosage. The most effective dosage regimen against active ulcerating renal lesions when streptomycin alone was used, was 0.3 gm. every 4 hours day and night for 120 days. As the dosage or time of treatment were lessened, the effectiveness decreased. Forty-two day regimens were inadequate.

Large renal lesions responded poorly. Most patients with renal tuberculosis were not discovered until their lesions were large enough to be definitely visible in the pyelogram. Any lesion which was visible in the pyelogram probably contained necrotic and fibrous tissue and was classified as a large renal lesion, even if only one calyx was involved. In this group of patients tubercle bacilli disappeared from the urine in only 25 per cent of the cases although in many additional instances the progress of the disease was apparently slowed or halted. Surgery was preferred for such renal lesions if the active disease was unilateral.

Small renal lesions responded well. The rare tuberculous kidney lesion which was discovered by means of a positive ureteral urine before there was a visible pyelographic lesion probably contained less necrotic and fibrous tissue. In our pilot series, 8 out of 10 such kidneys became consistently negative and the remaining two are probably negative.

Cystitis and ureteritis, Superficial ulcerations and edema responded well to streptomycin treatment. Contracted bladders and strictures due to deep seated fibrous lesions did not improve. Streptomycin treatment did appear to hasten fibrosis in rare cases.

Prostatic and epididymal tuberculosis did not respond sufficiently well to merit the use of streptomycin except where severe cystitis had resulted from local extension of the lesion into the bladder. Epididymal tuberculosis was preferably treated by surgery, accompanied by 3 weeks of streptomycin.

Limitations. The development of resistance and the presence of necrotic, caseous or fibrous tissue were the chief limiting factors. If treatment was started early enough the results were excellent.

Surgery was preferable to streptomycin for large tuberculous lesions of the kidney or epididymis containing necrotic tissue. A 3 weeks' course of streptomycin, 0.5 gm. every 12 hours, was given at the time of any operation upon a tuberculous organ.

Combined therapy using streptomycin and PAS is now under investigation and appears promising.

CONCLUSION

Streptomycin alone is sufficiently effective to be useful against bilateral, solitary and selected small unilateral renal tuberculous lesions. It is hoped that toxicity can be reduced and effectiveness increased by combined treatment with other tuberculostatic drugs such as para-aminosalicylic acid.

Our bacteriologist Milton Goldman, head nurse Lydia R. Sechler and her staff, our secretary Miss Alfreda Jastremski, illustrators Shapiro, Barlow and staff, and the departments of Pathology, Roentgenology, Otalaryngology, Medicine, Urology and Corrective Therapy, have been most helpful in this work.

We wish to express our appreciation to consultant Dr. Archie L. Dean for sponsoring this presentation.

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DISCUSSION

Dr. George E. Slotkin (Buffalo, N. Y.): I did not have an opportunity of reviewing the presentation by Drs. Lattimer and Dean until today. Of necessity, therefore, my remarks must be confined to the excerpt which appeared in the program.

The results which the essayists have obtained over a 120 day period of treatment are good, and a shorter regime is inadequate; but by their own admission, they are testing other preparations either singly or in combination, I assume, in order to reduce the toxicity of the treatment, or arrive at a more satisfactory combination.

The plan which I advocated a year and a half ago and which has been published in both the *Journal of Urology* and the *New York State Medical Journal,* the combined use of small doses of streptomycin, a maximum of ½ gm. daily with the esters of chaulmoogra oil, and based on the premise that the oil conditions the bacillus and prepares the same for more lethal action by streptomycin, has been proven by in vitro, in vivo studies and by other clinicians. This hypothesis is elaborated in the exhibit at this meeting and employs the principle proven by Woods and Kilts, that there exists a comparative inhibition by the action of chaulmoogric acid. The inhibitory agent, chaulmoogric acid, closely resembles the essential metabolite tuberculostearic acid which is synthesized by both lepra and tubercle bacilli. The chaulmoogric acids are absorbed by the tubercle bacillus reducing the surface tension. This action results in competition between the drug and the essential metabolites. There is a depression of the enzyme system necessary for the production of the latter. A destructive respiratory action is indicated by the results of the in vitro tests.

In a large series of animals that were treated by the combined treatment as compared to streptomycin, the proportion of negative results was 5 times greater than by streptomycin alone. In a large series of 17 groups, 2 out of each 17 were negative after 10 weeks with streptomycin alone, 16,000 units per day; 10 out of 17 were negative by the combined use of streptomycin and chaulmoogra oil.

Employing fatty acids of various oils: cottonseed, linseed, coconut, and other oils, recommended by Dr. Lattimer, the bacteriocidal limit was zero to tuberculosis; whereas in concentrations of 1 to 32,000 with chaulmoogric acid, the bacteriocidal limit showed no growth.

It has also been shown both experimentally and clinically that by combining chaulmoogrates and streptomycin and diasone, that the bacterium was inhibited 400 per cent greater with eventual complete lethal action, as compared to streptomycin alone.

Our clinical results to date disclose: In the period from January 1, 1947 to January 1, 1949, 37 cases have been treated; 5 had the disease for 20 years and over; 16, 10 to 20 years; 11, over 10 years; and 5, under 5 years.

In 29 of the cases, bilateral renal tuberculosis was present. In 8 they were complicated by lower tract involvement, and in 4, the epididymis alone. Seven of the cases had previous nephrectomies. Ten had been in a sanatorium from 2 had previous streptomycin treatment alone without any the 37 cases, negative urine was obtained by the use of one course atment alone. Two courses were required in 7 cases and 3 courses in 3 cases. Each course involved a period of 35 days. In all but 2 of the cases to date, negative urines have resulted and remained negative with marked clinical improvement, healed sinuses and negative sputi finally achieved.

As a last word, I do not believe this is the final treatment in tuberculosis. I think, as Drs. Lattimer and Dean do, that there will be other combinations, but our results and the results of others have shown that to date we feel this is the best type of treatment we have to offer.

Dr. Rollin G. Wyrens (Seattle, Wash.): I have been following the work of Drs. Lattimer and Dean with a great deal of interest, because I consider it some of the best in this field of urology, well controlled and very authoritative in nature.

It has been my good fortune, for the past few years, to act as the urologic consultant at the King County Tuberculosis Hospital in Seattle, where many of the urologic problems are referred from the whole state of Washington as well as King County itself. Here, our handling of the problem has been very greatly influenced by their observations.

I would like to mention a few points about one phase of the use of streptomycin in the treatment of genito-urinary tuberculosis which I have observed and, I am sure, have been observed by many others. These concern its use in conjunction with surgery, and, by its use, the increase in the surgical indications in selected cases.

As others, we consider every case of renal tuberculosis as bilateral. We almost routinely prescribe streptomycin for 1 week preoperatively and for varying gths of time postoperatively, not only for nephrectomies but for any form of rgery for genito-urinary tuberculosis. From clinical observations, we now vor the longer duration of therapy. In cases for nephrectomy, the purpose is arily to try to cure the so-called normal kidney. Besides, as has been obed by the chest surgeons, our operative wounds in the 12 to 14 cases managed is way have, almost without exception, healed by primary intention and healed.

hermore, the immediate postoperative convalescence was smooth, and, without exception, the temperature did not rise above 101 F and fever t more than 3 to 4 days. This was true even in the more acute cases tients previously so often had shown a postoperative spiking fever to many days, and occasionally ended up with a disseminated form of

in which the patient presented a difficult operation, I accidentally moderate sized psoas abscess from a Pott's disease which we knew Penrose drain was inserted into the wound for 5 to 6 days, and ound healed like the rest and has remained so to the present date, east 6 months.

t with bilateral renal tuberculosis was operated upon as an emergan acutely obstructed upper ureter due to calcareous debris, through which I was unable to pass a ureteral catheter, cystoscopically. A nephrectomy was performed in view of the serious involvement found at operation and the history of repeated colics. In bluntly separating the adherent kidney pelvis from the underlying muscle, it was torn, and a large quantity of typical tuberculous pus welled up in the wound. That wound too, healed by primary intention in the usual time expected for a nephrectomy for nontuberculous lesions of uncomplicated nature.

When other indications are present, I would not refuse a patient a nephrectomy who presents only a positive culture, guinea pig or even stain for tuberculosis, and even in a few cases, mild pyuria from the urine from the better kidney, if good roentgenograms reveal no change indicative of tuberculosis. We may be wrong but, to date, with our few cases, I have been encouraged. Perhaps in time one should include some with more pyuria or even with mild pyelographic changes.

DR. JOHN K. LATTIMER (New York, N. Y.): Considerable doubt still exists as to whether Moogrol adds anything to the action of streptomycin alone. The tuberculosis people tried chaulmoogra oil years ago and found it useless against tuberculosis. They have also given up the idea of the "waxy" capsule which chaulmoogra oil is alleged to "dissolve." At the annual meeting of the National Tuberculosis Association a few weeks ago, I asked Dr. Selman Waksman, the discoverer of streptomycin, who spends most of his time in his fine laboratory testing various drugs against tuberculosis, if he had tried chaulmoogra oil. He replied that he had, but that his results were disappointing. The concluding sentence of his letter read, and I quote: "The results with this drug did not appear to be encouraging and this experiment was discontinued."

The idea of combining another drug with streptomycin is a fine one, but a more potent tuberculostatic drug, such as paraminosalycilic acid, would seem more logical than Moogrol. A combination of streptomycin and Promizole has proven inadequate in our experience.

When you use streptomycin, use it in adequate dosage. You must remember that streptomycin is a "one chance" drug. You have only one chance to really arrest the disease with it. If you give an inadequate dose you may render the organisms resistant and thus deprive that patient of his only weapon against the miliary, meningeal or renal tuberculosis which eventually kills so many of these people. Do not worry about the dizziness many of them will have. It is a small enough price to pay, if you can check their disease. We can give corrective exercises, for that matter, which will counter the ataxia to a great degree.

Our original group of 25 patients, many with huge renal lesions, treated with streptomycin alone, have not been followed for from 2 to 3 years. All are alive and in fair condition. This is so different from the statistics of the pre-streptomycin days that we are beginning to wonder if streptomycin has in some way altered the lethal nature of the disease, even where it has not eradicated the tubercle bacilli from the urine.

Aureomycin and Chloromycetin are said to have no effect upon renal tuberculosis. Still more effective regimens than those discussed here are on their way, however. I believe that the one for you to watch is the combination of streptomycin and paraminosalycilic acid (PAS).

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A CLINICAL EVALUATION OF GANTRISIN (NU-445)[1, 2]

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Compounds related to Gantrisin (3,4-dimethyl-5-sulfanilamido-isoxazole) were first synthesized by Backer and de Jonge. Their compound (3-methyl-5-sulfanilamido-isoxazole) showed only slight anti-coccal activity. Anderson noted from in vivo studies that this compound showed appreciable activity against E. coli. Gantrisin was then prepared in the Hoffmann-LaRoche Chemical Research Laboratories by M. Heffer and H. M. Wrest. Schnitzer subsequently studied this compound and reported on its solubility in the physiologically important range of *p*H 6.0–8.0. No evidence of kidney damage was found in rats and rabbits after prolonged treatment with Gantrisin. From his experiments with the more important gram negative and gram positive pathogenic organisms, both in vitro and in vivo, he concluded that "the therapeutic potentialities of the compound compared favorably with those of known and clinical useful sulfonamides."

Five reports in the literature record clinical experience with this drug. Sarnoff effected 9 bacteriological cures in 14 cases of Proteus infection and 2 additional cases were influenced favorably. The dose was 5–8 gm. per day with totals varying from 50–112 gm. given over a 10 day period. Narius reported 18 cures (36 per cent) in 50 cases of urinary tract infections caused by gram negative bacilli, while Rogers and Colby reported improvement in 7 of 20 cases of urinary infection by gram negative organisms with Gantrisin treatment. Haines and Micheli obtained 5 cures in 8 cases of urinary infection caused by the Proteus bacillus. Two cases were improved and 1 was a failure. No untoward reactions or changes in the blood were noted. Their schedule was 3 gm. as an initial dose and 2 gm. every 8 hours. In a controlled series of 60 cases reported by Fergusson and associates, 30 cases were treated with Gantrisin and 30 with sulphamezathine. Initial doses of 3 gm. followed by 2 gm. at 8 hour intervals were given until 31 gm. had been taken. Alternate cases received similar doses of Gantrisin and sulphamezathine. Gantrisin achieved more rapid bacteriostasis than sulphamezathine in uncomplicated cases of pyelonephritis. In the cases proving resistant to the latter drug, Gantrisin rapidly cleared the infection. No toxic reactions, crystalluria or other side effects were noted.

Our study includes 31 patients with infections caused by gram negative bacilli. Only cases which we believed would not or had not responded to other types of therapy were treated. In most cases at least 2 or more cultures were obtained before instituting therapy. The leukocyte count, urinary sediment, blood nonprotein nitrogen, blood sulfonamide level, and cultures were checked 2 to 3 times a week. In 17 patients the drug was given over a period of 9 to 13 days.

[1] The Gantrisin (NU-445) used in this study was supplied by Hoffmann-LaRoche, Inc.

[2] This investigation was supported with funds from the Dr. Henry C. Buswell Memorial.

In 9 patients the period of administration varied between 3 and 30 days. In 5 cases the drug was discontinued because of 1) coma, due to the disease under treatment 2) severe reactions, and 3) lack of cooperation in taking the drug. These 5 cases have been omitted from consideration of the therapeutic effect but are considered in the untoward reactions.

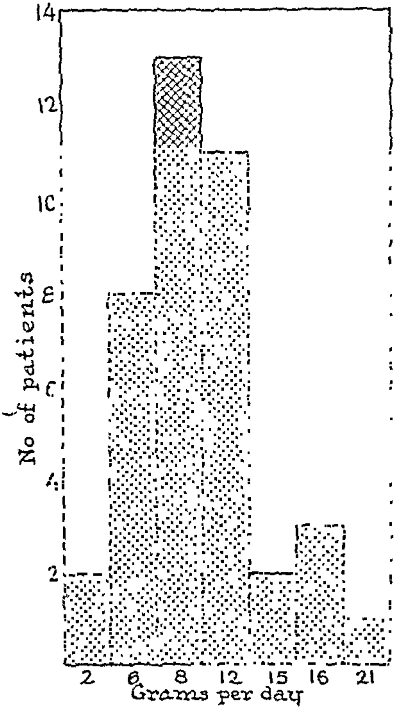

FIG. 1. Some of the 31 patients treated are represented in two columns as they received two courses of therapy or the daily dose was changed according to their response to treatment. This accounts for the apparent discrepancy between 31 patients treated and 40 patients as shown in the chart.

The dosage varied between 2 and 21 gm. a day (fig. 1). The latter dose was reduced after 2 days to 12 gm. a day because of a reaction. The *average total* dose administered to 29 patients was 83.4 gm. The minimum total dose was 24 gm. and the maximum 168 gm. The remaining patients received 283 gm. and 360 gm. (fig. 2). Some of the patients required 2 courses of therapy and in others the dose schedule was changed according to the response of the patient. All of the patients received Gantrisin orally but 2 of them also received intramuscular and intravenous injections. The intravenous administration was well tolerated but the intramuscular injection caused marked burning, stinging, and residual soreness.

The response to therapy is shown in tables 1 and 2. A cure demonstrated by 2 negative cultures at least 3 days apart was effected in 8 cases. In cases 7 and 12 the bacillary infection disappeared and a non-hemolytic streptococcus remained. Penicillin was given and the streptococcus was eliminated. In case 27 Psuedomona aeruginose (B. pyocyaneus), was grown from the patient's blood after 7 days of streptomycin therapy and there were no signs of clinical improvement. Gantrisin was given and his temperature became normal in 48 hours and all subsequent blood cultures were negative. His urine continued to contain Psuedomona aeruginosa.

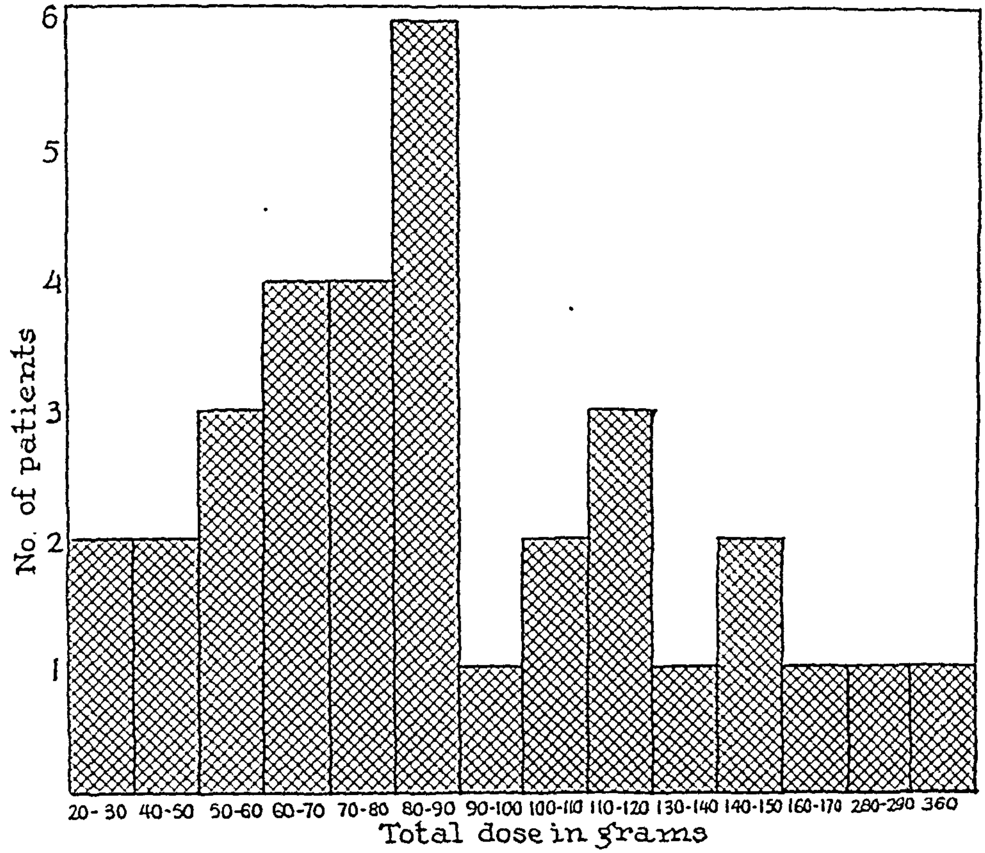

Fig. 2

An example of an excellent clinical response to Gantrisin follows:

Case 26, S. M. H. 122,402, an 18 year old white man was admitted on April 2, 1947 with second and third degree burns of both hands, wrists, lower abdomen, scrotum, penis and buttocks. The burned areas were treated by debridement and irrigation followed by vaseline gauze and massive compression dressings of mechanics waste. Plasma, whole blood, and Ringer's solution were administered as indicated. He was given penicillin 50,000 units every 3 hours and sulfadiazine,

TABLE 1.—*Results of treatment of 31 patients*

CASE	DIAGNOSIS	SPECIMEN	BACTERIUM	C.	P.	I.	D.
1	Cystitis, chronic; prostatitis, chronic.	Urine	E. coli			x	
2	Cystitis, chronic.	Urine	E. coli	x			
3	Osteomyelitis of the tibia, chronic.	Wound	E. coli			x	
4	Cystitis, chronic; median bar; residual urine 120 cc.	Urine	Proteus			x	
5	Cystitis, chronic; post-perineal prostatectomy.	Urine	E. coli			x	
6	Cystitis, chronic; post-perineal prostatectomy.	Urine	E. coli				x
7	Pyelonephritis, chronic; contracture of vesical neck.	Urine	Pseudomona aeruginosa	x			
8	Cystitis, chronic; post-perineal prostatectomy.	Urine	E. coli			x	
9	Pyelonephritis, acute and chronic; carcinoma of the bladder; nephrostomy, right.	Urine	E. coli Proteus				x
10	Scrotal abscess following vasectomy.	Wound	Proteus	x			
11	Pyelonephritis, chronic; pulmonary tuberculosis.	Urine	E. coli				x
12	Pyelonephritis, chronic; urethral obstruction.	Urine	E. coli	x			
13	Pyelonephritis, chronic; double kidney, right.	Urine	E. coli	x			
14	Pyelonephritis, chronic; diabetes mellitus.	Urine	E. coli		x		
15	Multiple malignant papillomas of bladder; urinary extravasation; retrovesical abscess.	Wound Blood	Proteus			x	
16	Pyelonephritis, chronic; diabetes mellitus; portal hypertension.	Urine	E. coli			x	
17	Cystitis, chronic.	Urine	Pseudomona aeruginosa			x	
18	Pyelonephritis, chronic; bilateral ureteral strictures.	Urine	Pseudomona aeruginosa				x
19	Cystitis, chronic; prostatitis, chronic; urethral stricture.	Urine	Aerobacter aerogenes			x	
20	Pyelonephritis, chronic; hydronephrosis, bilateral.	Urine	Pseudomona aeruginosa			x	
21	Pyelonephritis, chronic; cystitis, chronic.	Urine	Aerobacter aerogenes		x		
22	Amputation of left leg for arteriosclerotic gangrene; septicemia; wound infection.	Blood	E. coli	x			
23	Wound infection following spinal fusion.	Wound	Proteus			x	
24	Abscess of pancreas and abdominal wall; septicemia.	Wound Blood	Proteus		x		
25	Transurethral prostatectomy; suprapubic cystostomy; septicemia.	Blood Urine	Aerobacter aerogenes				x
26	Second degree burns of abdomen, thighs, penis, scrotum and perineum; septicemia.	Blood Urine	Pseudomona aeruginosa	x			
27	Renal plastic for hydronephrosis; pyelonephritis, chronic; septicemia.	Blood	Pseudomona aeruginosa	x			
28	Wound infection post-op. hip pinning for fracture of femoral neck.	Wound	Proteus			x	

TABLE 1.—*(Continued)*

CASE	DIAGNOSIS	SPECIMEN	BACTERIUM	C.	F.	I.	D.
29	Pyelonephritis, chronic; renal calculi, bilateral; cystitis, chronic; post-op. plastic on bladder.	Urine	Pseudomona aeruginosa		x		
30	Bilateral hydronephrosis and hydroureter; median bar; suprapubic cystostomy; abscess of kidney.	Urine	Pseudomona aeruginosa			x	
31	Paraplegia; pyelonephritis, chronic; cystitis, chronic.	Urine	E. coli		x		
Totals				8	5	13	5

Key: C—Cure; F—Failure; I—Improved; D—Deleted from final results.

TABLE 2.—*Summary of results*

	NO.	PER CENT	PSEUDOMONA AERUGINOSA	PROTEUS	E. COLI	AEROBACTER AEROGENES
Cures	8	30.8	3	1	4	0
Symptomatic response	7	27	2	1	3	1
Clinical response	6	23	1	3	2	0
Failures	5	19.2	1	1	2	1
Totals	26	100	7	6	11	2

1 gm. 4 times daily. A retention catheter was inserted because of the area involved by the burn. Adequate dietary measures were instituted. Wangensteen suction was started to control abdominal distention. The urinary output and blood pressure remained satisfactory. However the temperature varied between 38.6 C and 38.8 C for the first 4 days of his hospital stay.

He developed a Psuedomona aeruginosa infection of the burned areas and suffered numerous chills with temperature elevations up to 42°C. He became disoriented. Blood cultures on 2 successive days showed Psuedomona aeruginosa and a culture of his urine showed the same organism. Gantrisin was given and all subsequent blood cultures were negative. Within 48 hours his temperature began to decline (fig. 3), he became less toxic and his delirium cleared. Six days after starting the drug, when the dressings were changed, no evidence of Psuedomona infection could be detected in the burned areas.

From then on until discharge 6 weeks after admission, his course was uneventful. The burned areas healed satisfactorily. The Psuedomona aeruginosa was eliminated from his urine leaving a Gantrisin-resistant non-hemolytic streptococcus. The patient at no time showed any untoward reaction to the drug.

Seven patients obtained symptomatic relief characterized by a decrease in frequency, burning, dysuria and nocturia, a general feeling of well being and an increase in appetite although the urine cultures remained positive. Case 19 had marked decrease in his symptoms of frequency, burning and dysuria and stated "I haven't felt better in years." He was unable to tolerate other sulfonamides.

Clinical responses such as the cessation of chills and fever, the improvement in wound infections with decrease in drainage, and the production of healthy granulations, although the cultures remained positive, were noted in 6 patients. Case 31 developed a Proteus wound infection following the pinning of the right femur for a fracture of the neck. There was profuse, purulent drainage and the wound remained open. Gantrisin was given. In 48 hours there was only scant drainage and in a few days the wound was filling in with healthy granulations. The cultures remained positive for Proteus although the organism was sensitive to the drug. The pin was removed and an abscess pocket was found associated with it. The principal of combining adequate surgical drainage with chemotherapy must still be applied for maximum response to any chemotherapeutic or antibiotic agent.

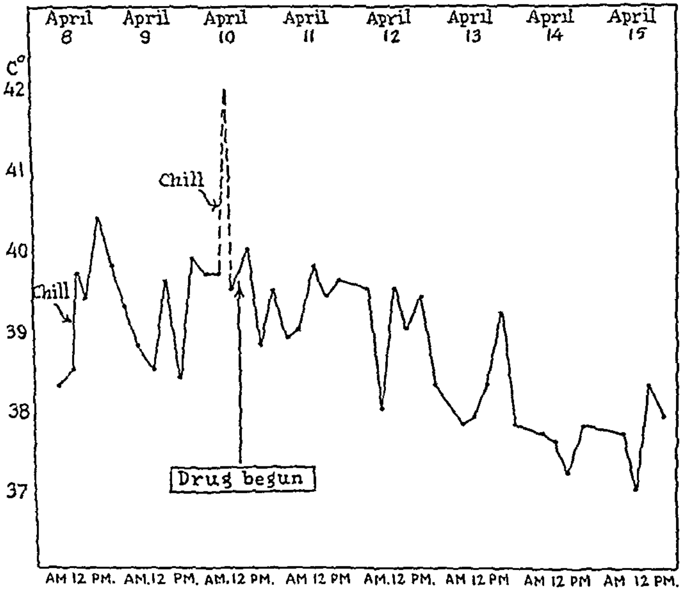

FIG. 3. Patient had Pseudomona aeruginosa infection of blood, urine, and burned area of body.

There were 5 absolute failures.

Hematuria was noted in 14 patients. In 13 cases it was microscopic and in only 5 could it be definitely related to the administration of the drug. The one case showing gross hematuria had a marked reaction and is discussed in detail later. No evidence of crystalluria was noted.

Leukopenia was found in 7 patients. This was independent of the size of the dose and occurred in those cases taking from 6 to 16 gm. a day. Of 17 patients in whom the differential leucocyte count was followed, 2 developed neutropenia.

The blood nonprotein nitrogen was essentially unaltered during therapy.

Untoward reactions were noted in 6 patients. Three were mild and 3 were moderately severe. None was fatal. The mild reactions consisted of slight headache, dreaming, loss of appetite, and light headedness. With the mild reactions there was no relation to the size of the dose whereas all cases with moderately severe reactions, the dose was 12 or more grams a day.

The three remaining patients had the following reactions:

One patient suffered from severe nausea, vomiting, and generalized macular rash which disappeared 2 days after the drug was discontinued. The dose in this instance was 12 gm. a day.

A second patient developed a decreased urinary output, facial edema and microscopic hematuria. This disappeared when the dose was reduced from 21 gm. to 12 gm. a day.

A third patient who had an Aerobacter aerogenes septicemia, acute pyelonephritis, and cystitis, following a transurethral prostatectomy, developed generalized edema, grossly bloody urine, toxemia, delirium, hypoprothrombinemia with petechiae and submucosal hemorrhages while receiving 16 gm. of Gantrisin a day. The drug was discontinued and supportive therapy with blood transfusions, calcium gluconate and vitamin C was administered. He showed marked improvement during the following 24 hours but succumbed to the septicemia 6 days later. Wheter or not the drug was responsible for these untoward reactions cannot be determined at this time.

It is interesting to note that the 3 patients showing moderately severe reactions to Gantrisin attained high blood levels of 18.7 mg. per cent, 25.5 mg. per cent and 22.1 mg. per cent in 2, 4, and 5 days respectively, while on a daily dose of 12 gm., 16 gm. and 21 gm. respectively. The average blood level for 12 gm. per day was 6.5 mg. per cent and 8.5 mg. per cent for 16 gm. per day. The remaining cases receiving comparable doses of the drug failed to show such marked elevations of their blood sulfa levels.

SUMMARY

All of the patients treated in this study either had previous therapy, or had developed their infection during treatment with other chemotherapeutic agents or antibiotics, or their infections were of sufficient severity to doubt that an effective response could be obtained by other methods of treatment. It was our opinion that improvement would constitute evidence of a therapeutic effect because of the inadequacy and ineffectiveness of other agents used against these gram-negative bacillary infections. Streptomycin is an exception to this statement. Three of the 7 cases of Psuedomona infection (43 per cent), 4 of the 11 cases of E. coli infections (36 per cent), and 1 of the 7 cases of Proteus infections (16.5 per cent) were cured of their infections following the administration of Gantrisin; an over all cure rate of 30.8 per cent. This compares favorably with Narius' report. Sarnoff mentioned that concomitant infections with E. coli and Psuedomona aeruginosa did not seem to be affected favorably by the therapy with Gantrisin. As they stated in their discussion, "The results presented leave a great deal to be desired."

Higher daily and total doses of Gantrisin have been used in this study than have been reported previously In general these amounts have been well tolerated However, 3 reactions of moderate severity have been noted but close observation of the patient plus the usual laboratory examinations of an individual receiving a sulfonamide prevented any unfortunate sequelae All reactions terminated soon after the drug was discontinued Our studies indicate that a reaction to the drug will probably manifest itself within 5 days of the initial administration and will be accompanied by an abnormally high blood level of Gantrisin

Sixteen grams daily in divided doses seems to be the highest dose which can be tolerated safely The effective dose however, seems to be between 8 to 12 gm daily Five of the 8 cases cured received 8 gm daily and 3 received 12 gm daily The administration of an initial large dose in an attempt to increase the blood level of Gantrisin did not appear to be effective When cultures of the offending organism were resistant to Gantrisin increasing the daily dose did not result in increased effectiveness of the drug Infections due to Gantrisin resistant organisms did not respond to treatment with the drug

CONCLUSIONS

Gantrisin is an effective chemotherapeutic agent in some infections caused by E coli, Psuedomona aeruginosa (B pyocyaneus), and Proteus bacilli

The effective dose of Gantrisin is 8–12 gm daily Sixteen grams daily in divided doses appears to be the maximum dose which can be safely administered

Reactions similar to those occurring with other sulfonamides occur during the administration of Gantrisin Crystalluria, however, was not observed either in an acid or alkaline urine

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A URETHRAL STRICTURE DETECTOR FOR USE IN THE FEMALE

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It has been our practice for a number of years to check thoroughly the urethra of every female who comes to us for diagnosis and treatment. We have customarily used bulb sounds for this purpose. The bulb sounds available were of the typical male length and about four or five were necessary for each case.

We conceived the idea that four bulbs, sizes 22, 24, 26 and 28F, could be incorporated on a short staff which would place the bulbs sufficiently far apart to diagnose strictures in the female urethra. This would give us one small, conveniently sterilized instrument which would be readily available and which would be thoroughly satisfactory to make this very important test.

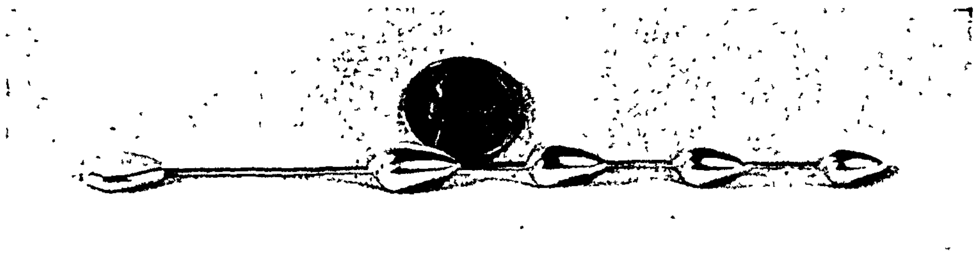

FIG. 1

We have used the instrument (fig. 1) for several months and find it very useful. We believe that it is a worthwhile addition to the urologist's armamentarium, and we hope that with its use a great many urethral strictures which now go undetected will be diagnosed and cured.

We find that a simple meatotomy done after the technique advocated by McDonald of Atlanta is curative in almost 100 per cent of the cases.

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XYLOCAINE: A NEW TOPICAL ANESTHETIC IN UROLOGY[1]

J. S. HAINES AND HARRY GRABSTALD
From United States Marine Hospital, Baltimore, Md.

Several months ago the urology service at this hospital began to investigate a new anesthetic drug. This new drug called Xylocaine (diethylamino-2.6 diethylacetanalide) was first described by Löfgren and Lundquist of Sweden and its pharmacological properties were studied by Goldberg, who compared it with procaine and tetrocaine as to toxicity, action on blood pressure, anesthetic qualities, including its use as a topical anesthetic, and local irritant action. He concluded that Xylocaine showed high degrees of anesthetic potency both for surface and infiltration purposes and that it displayed a combination of pharmacological properties which strongly urged its use for clinical purposes.

Of the many qualities desirable in an anesthetic, including low toxicity and effective interruption of painful stimuli, rapidity of action is especially important to the urologist who would prefer to be able to do cystoscopy without having to wait for long periods of time, while an anesthetic agent is taking effect. We believe that Xylocaine has these favorable attributes.

We have used Xylocaine in a 2 per cent solution as a topical anesthetic for transurethral procedures varying from mere passage of sounds to cystoscopy with extensive fulguration of bladder papillomas. Our results have been highly satisfactory and we have noted no untoward reactions. Approximately 10 cc are used for each cystoscopy except in females in whom Xylocaine soaked applicator sticks have been successfully used. It is extremely difficult to evaluate an anesthetic agent in cystoscopy wherein so much depends upon subjective differences as well as upon the technique and skill of the operator. In our series of 250 cases, we have made a special point of including those patients who had had previous cystoscopy either at this hospital or elsewhere when Xylocaine was not used. Almost without exception, these patients have expressed a definite preference for the procedure in which Xylocaine was used. In many instances the same operator had occasion to examine these patients with and without the benefit of Xylocaine and the results were rather decisive in favor of this agent.

Several cases in our series are worthy of mention. One 75 year old physician who had had recurrent bladder papillomas fulgurated at regular intervals under spinal anesthesia entered the hospital for treatment and refused spinal on this occasion. Highly satisfactory anesthesia was obtained using Xylocaine and approximately 15 bladder papillomas were fulgurated successfully. Two veterans who had suffered straddle injuries and ruptured urethras during the war have been coming to this hospital at regular intervals for urethral dilatations for several years. These men have both reported a definite difference and improvement following use of Xylocaine.

---

[1] The Xylocaine used in this study was furnished by Mr. Erik Bjaringer of the Astra Pharmaceutical Products.

Without exception definite subjective differences have been noted in those in whom cystoscopy is done with Xylocaine on one occasion and with other topical anesthetics on others.

Several months ago under the Section titled Queries and Minor Notes in the Journal of the American Medical Association a physician reported on the use of "Zylcaine" in local anesthesia. This product is stated "to contain in each cc procaine base, 0.075 gm.; Butyl aminobenzoate, 0.3 gm.; and benzyl alcohol, 0.25 gm., dissolved in peanut oil." This material is a long lasting anesthetic which has apparently produced some local untoward reactions. This agent is not the one described in this paper. The similarities in names justifies this brief comment.

SUMMARY

Xylocaine, a new topical anesthetic, has been used in some 250 cystoscopies without untoward results and with good, rapid anesthesia. Further clinical trial is warranted.

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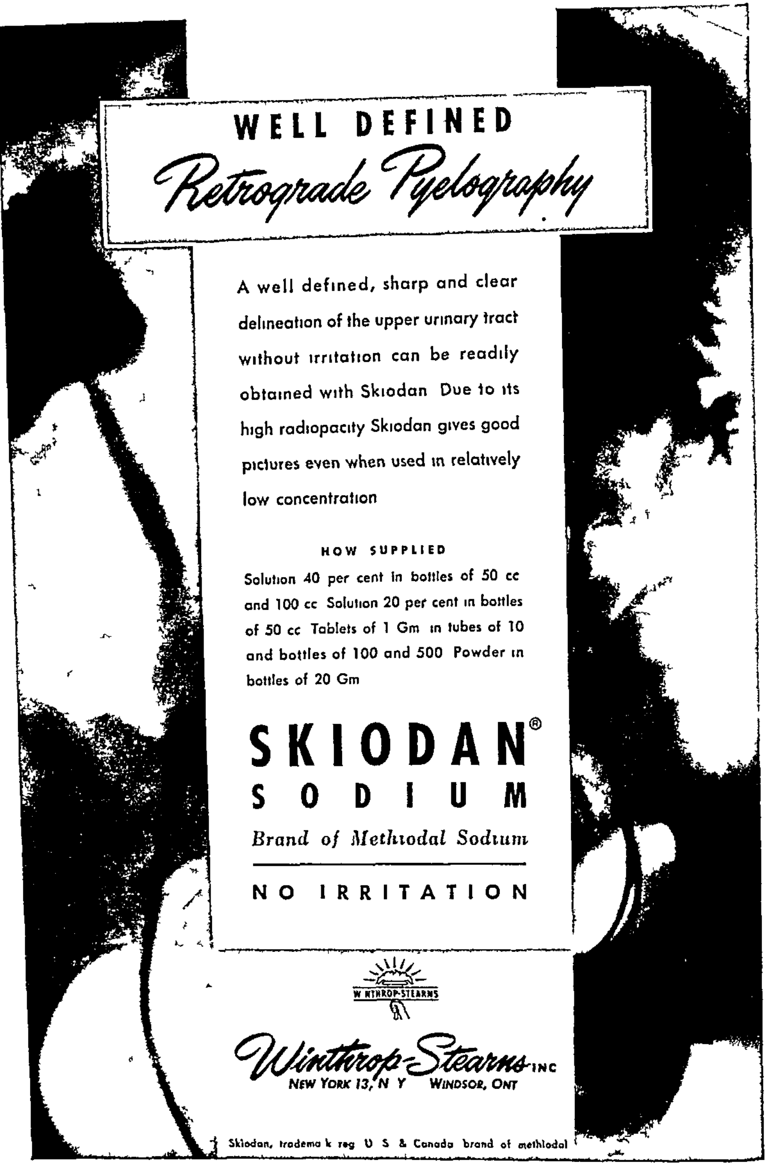

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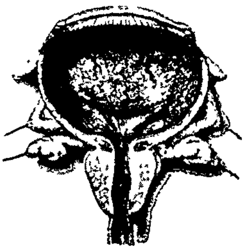

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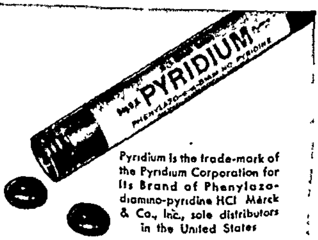

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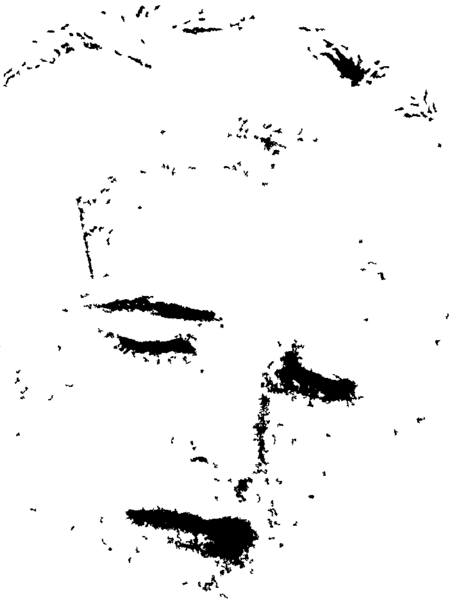

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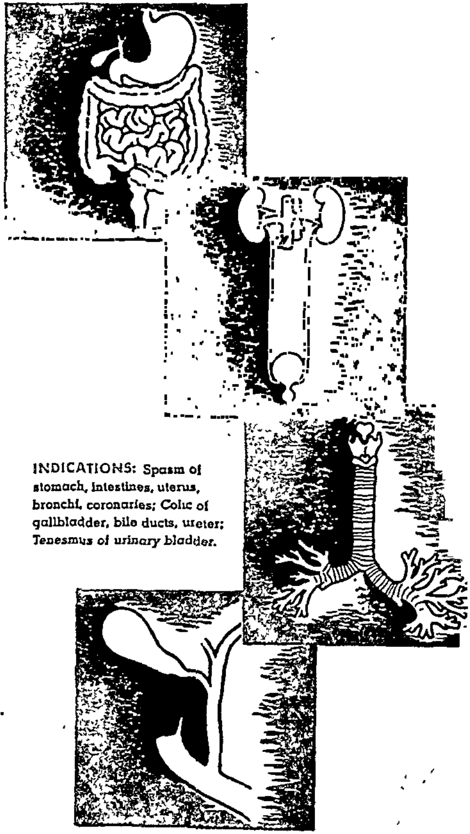

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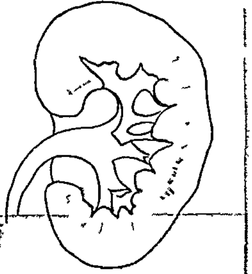

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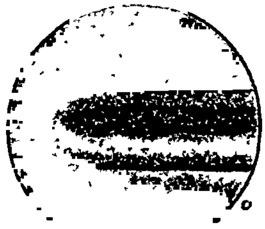

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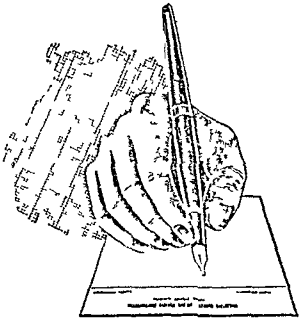

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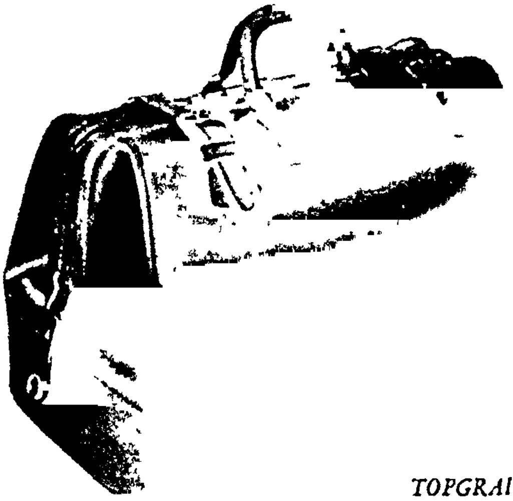

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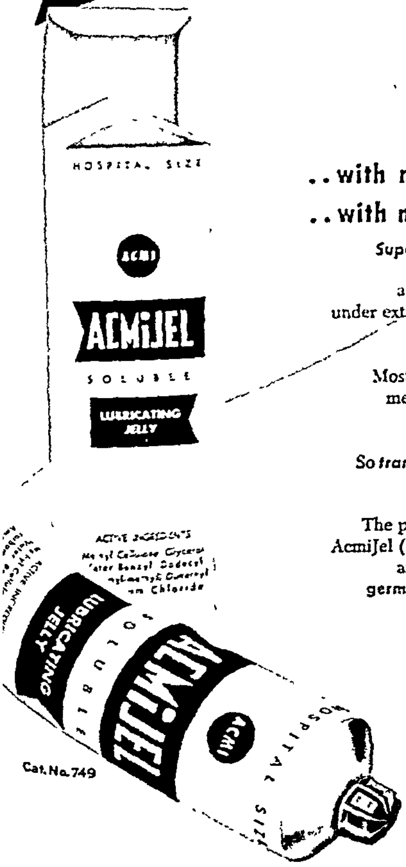

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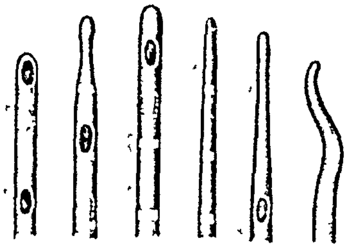

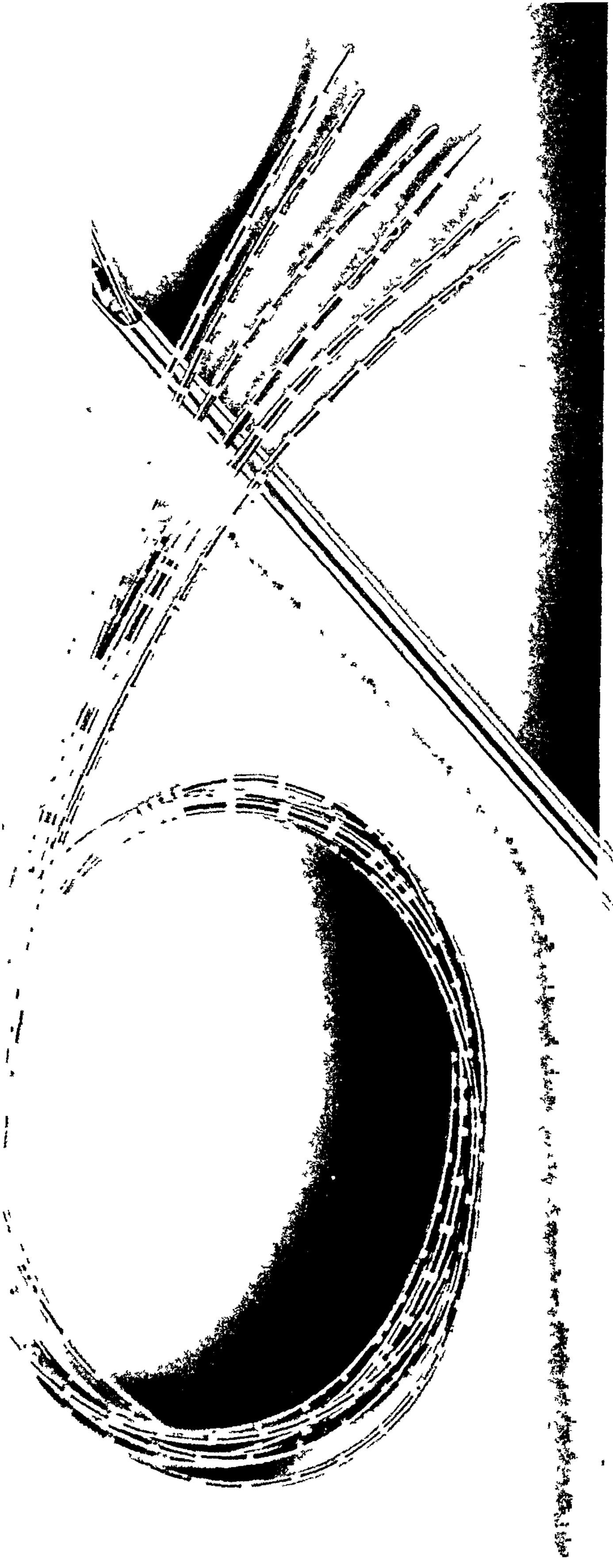

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CALCULOUS PYONEPHROSIS ASSOCIATED WITH SQUAMOUS CELL CARCINOMA OF THE RENAL PELVIS

ROBERT L. ATKINSON

The history of the case herein reported concerns a housewife, aged 64, who was bothered by cramping abdominal pain which was variable in its severity and which was first noticed about 6 months before admission to the hospital. This pain started just to the left of the umbilicus and radiated downward anteriorly towards the midline. There was a definite relationship of the pain to rather marked nervousness and fatigue, and frequency of urination. No hematuria was noted at any time and there never was any nausea or vomiting. The first doctor whom the patient consulted diagnosed the disease as colitis and prescribed a low roughage diet; and for the urinary frequency, belladonna and phenobarbital were given in the belief that this symptom was due to the nervousness. X-rays of the gastro-intestinal tract were reported to the patient as being normal.

The bedside physical examination revealed a well nourished white woman who was not actually ill, but who had moderately severe, diffuse, deep tenderness in the abdomen to the left of the umbilicus. The other physical findings were noncontributory.

Microscopic examination of the urine revealed many pus cells and many red blood cells. On urine culture E. coli were isolated.

Intravenous urogram showed the left kidney to be nonfunctioning and containing multiple calculi (fig. 1). Cystoscopy disclosed evidence of chronic infection, manifested by granulation tissue near the left ureteral orifice. Through a 6 F ureteral catheter a rather profuse flow of dark, foul-smelling purulent material was obtained, which on culture produced a pure growth of E. coli.

Removal of the left kidney was performed through the usual lumbar approach (Dr. James I. Farrell, surgeon).

Upon sectioning the gross specimen of kidney, a large amount of an admixture of stones and pus poured out of the pelvis as the knife passed through it. After the kidney pelvis was cleansed, a firm, pink-grey, ovoid mass measuring 3.5 cm. in diameter was found to be occupying most of the pelvic cavity and occluding the ureteral outlet (fig. 2). The renal artery and vein were not involved.

Microscopically the tumor was found to be made up of stratified squamous epithelium and many areas of pearl formation (fig. 3). The ureter showed only chronic inflammation.

Following the nephrectomy, the patient had complete relief of [illegible] mptoms for about 2 months, but then there developed a rat [illegible] ere aching pain in the left hypogastrium and nephrect [illegible] pain required increasing amounts of opiates, the patient [illegible] hospital. During this second admission, surgical explorat [illegible] disclosed a large tumor mass which on microscopic exami [illegible] a squamous cell carcinoma. Being unable to control t [illegible]

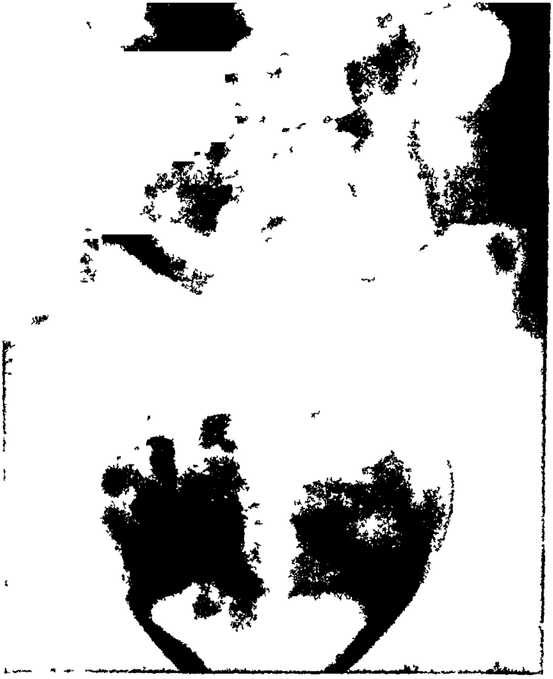

FIG. 1. Intravenous urogram (10 minute film), showing nonfunctioning left kidney and mass of stones in renal pelvis.

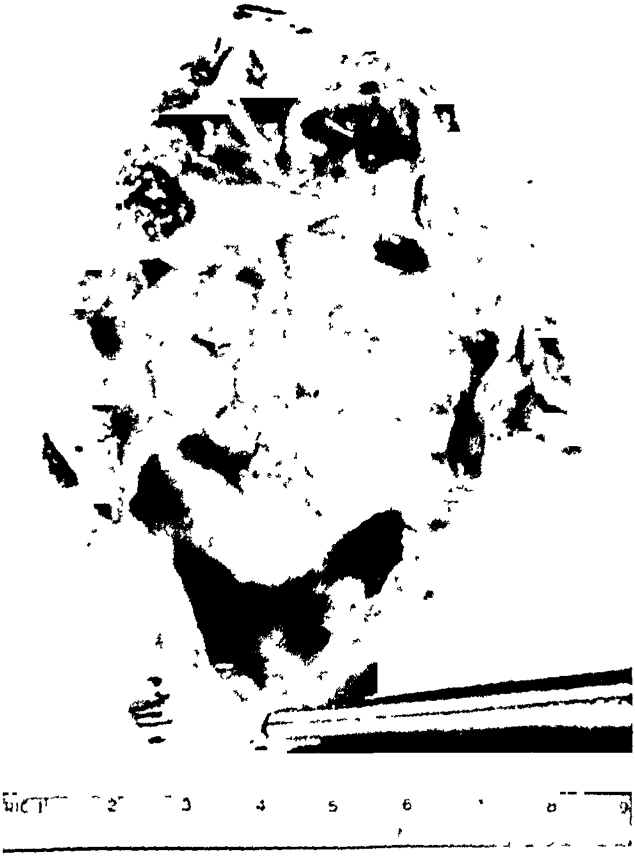

FIG. 2. Specimen after removal of calculi. Note pelvic tumor and marked hydronephrosis

of pain suffered by the patient, a bilateral chordotomy was done which gave temporary relief,

In spite of 1500 r of radiation, the course of the illness was downhill with rapid wasting away in the last few days of life. The patient died about 20 months after the onset of the terminal illness.

The autopsy revealed a necrotic tumor mass in the left renal fossa which had invaded and destroyed the adjacent vertebral bodies. Other metastatic lesions were found in the pancreas, left adrenal and periaortic nodes.

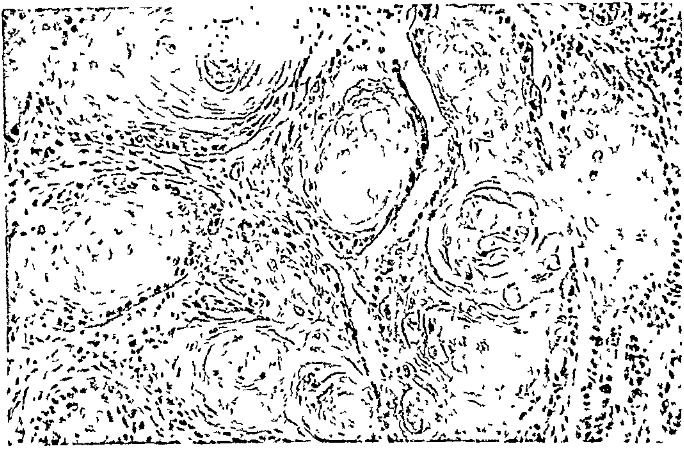

FIG. 3. Low power photomicrograph showing squamous cell carcinoma with pearl formation.

COMMENT AND DISCUSSION

The most valuable commentary on this case brings out the fact that the patient had been treated for a considerably long period of time for a disease which she did not have, namely, colitis. The calculous pyonephrosis which she did have and which led to her death should have been diagnosed, or at least suspected at the time the first x-ray film of her abdomen was made. It will be recalled that the physician who treated the patient for colitis reported to her that the gastro-intestinal x-ray series showed nothing abnormal No mention was made of the shadows cast by the renal calculi. It is possible that these stones were obscured by overlying barium in the bowel.

The physiological interrelation of the urinary tract and gastro-intestinal tract by way of the coeliac and hypogastric plexuses explains the gastro-intestinal manifestations of renal and ureteral pathological changes seen in some cases of urinary tract disease. This case is a good example of renal disease, the chief symptom of which was chronic abdominal pain.

With regard to the differential diagnosis of radiopaque material in the plane of the left kidney, one should bear in mind such things as calcified mesenteric lymph nodes, calcifications of the splenic artery, calcified aortic aneurysm, and, more rarely, stones in the tail of the pancreas. In most instances there will be little difficulty in diagnosing a renal pelvis filled with stones.

It cannot be determined how long the calculi had been present, but it is safe to assume they were of long duration. At any rate, they had been present long enough to destroy kidney function. As regards the chronicity of the tumor no one knows when it started to grow. Martin and Mertz, in their series of 108 cases of all types of kidney cancer associated with stones, stated the average duration of symptoms due to the stones to be 19 years and the duration of symptoms due to the tumor to be about 5 months.

Squamous cell carcinoma of the renal pelvis is not common. This statement has been made many times by various writers, among them being Kickham and Stanton and Swift-Joly. In 1944 Melicow at the Squire Urological Clinic brought the total number of reported cases up to 75. The diagram in figure 4 will help to category this tumor. Squamous cell carcinoma of the renal pelvis associated with stones is less common than the tumor alone. Gilbert and Macmillan in 1934 reported 52 per cent of 57 cases studied associated with stones. It is well known that there is a striking relationship of renal pelvic squamous cell cancer to long-standing infection and stones which probably irritate the pelvic mucosa causing its metaplasia to squamous epithelium and then its growth into a cancer.

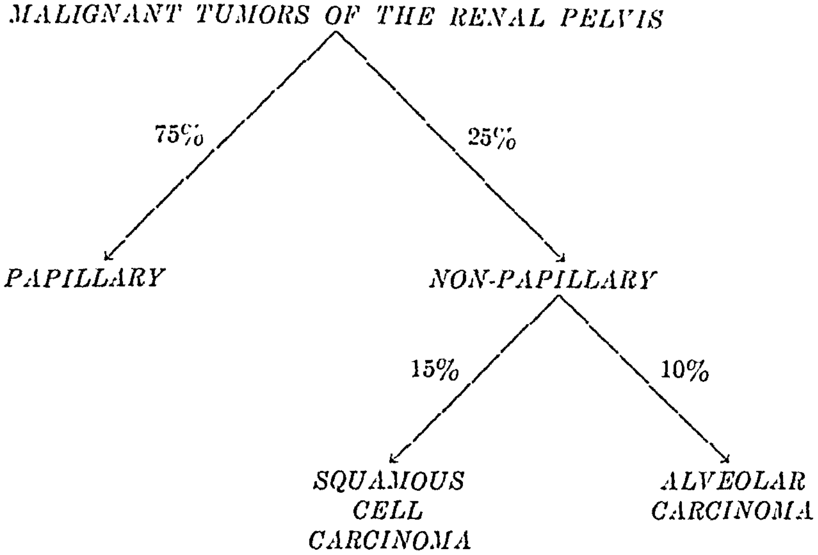

FIG. 4. Classification of renal pelvic tumors

The difficulties of accurately making a preoperative diagnosis of this tumor have been pointed out by Gilbert and Macmillan in the previously mentioned 57 cases they reported. They found the various diagnoses to be kidney tumor in 20 cases; kidney stones in 20 cases; no diagnosis in 11 instances; pyonephrosis in 3 cases; renal tuberculosis in 1 case and, 1 case was diagnosed as cystic ovary. This totals 56 cases. One of their cases was accurately diagnosed preoperatively as squamous cell carcinoma of the renal pelvis.

SUMMARY AND CONCLUSIONS

In summary, then, we have a case of a 64 year old woman with long standing abdominal pain which was believed to be chronic colitis associated with nervousness and treated accordingly Urological examination disclosed the true nature of the illness to be calculous pyonephrosis Nephrectomy and subsequent pathological examination of the kidney revealed a highly malignant pelvic tumor which led to the patient's demise Here, as in all of the branches of the practice of medicine, thoroughness and completeness of examination still are, and always will be, of the utmost importance

1520 N Clinton Blvd , Bloomington, Ill.

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CUS PRODUCING ADENOCARCINOMA OF THE RENAL PELVIS

ALEX B. RAGINS AND HARRY C. ROLNICK

From the Departments of Urology and Surgical Pathology, Cook County Hospital, Chicago, Ill.

Ialignant tumors of the pelvis of the kidney are extremely rare[1]. Bell[2] in his of 30,000 autopsies found 154 renal tumors, an incidence of 0.51 per cent. the 154 renal neoplasms reviewed, only 4 or 2.6 per cent were of pelvic origin. ann[3], in his analysis of 3499 renal neoplasms found 226 cases, or 6.2 cent arising in the renal pelvis. This incidence is a little more than twice found in Bell's studies.

In the past 19 years (July 1928 to July 1947), 936 kidneys were removed gically at the Cook County Hospital, and of these 122 or 13.8 per cent were neoplasms. Of these 13 or 10.7 per cent were of pelvic origin. One of the ors arising in the pelvis proved to be a mucus producing adenocarcinoma, a ion of rare occurrence. In searching the literature, we were successful in ding 2 additional cases, one reported by Plaut[4] and the other recently re- orted by Ackerman[5].

The rarity with which mucus producing adenocarcinomas arise in the renal pelvis, and because of the pathogenesis involved in explaining the presence of such a tumor in a renal pelvis, prompts our case report.

CASE REPORT

M. M., a Negress 51 years of age, was admitted to the Cook County Hospital on November 11, 1939, complaining of pain of 9 months' duration in the right lower quadrant and right lumbar region. During the month previous to admission the pain became more severe and more constant, and she found it necessary to hospitalize herself for treatment.

The temperature, pulse, and respirations were normal. The blood pressure was 116/78. The abdomen was obese; the liver, kidneys, and spleen were not palpated. Tenderness over the abdomen was absent, but a Murphy punch over the right kidney elicited a considerable amount of pain.

Urinalysis revealed 2 plus albumin. The nonprotein nitrogen was 26 mg./100 cc. The creatinine was 1.5 mg./100 cc, the blood sugar 78 mg./100 cc. The blood Kahn was negative.

X-ray of the chest showed bilateral increase of the hilar markings and a small discrete area of calcification in the lung at the level of the fifth rib. A flat film of the abdomen revealed opaque shadows in the right renal area. An electrocardiogram showed a left ventricular preponderence.

A diagnosis of a right renal calculus was made.

---

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The essential urologic findings were: narrow right ureter, secretion of dye (phenosulphonphthalein) was absent from the right kidney after 30 minutes, whereas the left kidney secreted the dye in 6 minutes. Following cystoscopy a bilateral retrograde pyelogram revealed a coiled catheter in the left kidney with suggestive slight blunting of the calyces. The right pyelogram revealed a marked clubbing of the calyces associated with renal calculi (fig. 1) in the upper and lower poles of the kidney, but particularly in the superior calyx. In addition, there was a filling defect of the urinary bladder suggestive of a diverticulum on the left side.

On December 6, 1939 the patient underwent surgery for removal of the right kidney. After uneventful recovery over a period of 41 days she was discharged improved.

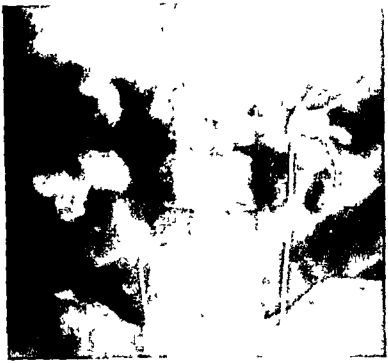

FIG. 1. Retrograde pyelogram, showing marked clubbing of calyces associated with renal calculi.

The specimen consisted of a right kidney surrounded and covered by adherent perirenal fat tissue. The kidney measured 8.5 by 8.5 by 4.0 cm. On sectioning, the capsule was found adherent to the surface of the kidney. The cortex was reduced to a thickness of 2 mm. The pelvis was dilated, and the calyces were flattened and filled by large fragments of a staghorn stone. The largest fragment measured 4.5 by 2.5 by 1.5 cm. and was located in the inferior major calyx and extended into the two minor calyces. The mucosa of the lower major calyx about the fragment of stone was reddish gray and granular. The cortex of the kidney in this region was narrowed, firm, and grayish white. The inferior minor calyces were lined by a light yellowish gray membrane and contained fragments of stone within the lumen. In one area of the lower minor calyx the surface was composed of a reddish gray, granular, gelatinous-like tissue which, on sectioning, appeared to extend into the medullary portion of the kidney for a distance of 4 mm. (fig. 2).

In the upper pole of the kidney the calyces contained small fragments of stone. The mucosa was thickened, purplish red, and granular. The urethral wall kened, and the mucosa was grayish white and mottled by areas of pale gray.

roscopic examinations were made of sections taken from the lower calyx by the gelatinous material, after being stained with hemalum and eosin, Gieson, and mucicarmin stain. Histological examination revealed the lin- brane to be composed of numerous large glands lined in some places by olumnar epithelium and in other places by stratified cuboidal epithelium 3,*A*). The nuclei of the cells varied in size and shape. Many of them were ted, while others were round or barrel shaped and lay close to the basement portion of the cell. Mitotic figures in the tumor tissue were fairly numerous, particularly in those tumor glands which had invaded into the stroma of the fibrotic kidney (fig. 3,*B*). The cytoplasm of many of these cells was filled with globules of mucin (fig. 3,*C*) which stained red with mucicarmin stain, as did the material lying free within the lumen of the dilated glands. In places there were small papillomatous proliferations into the lumen of the glands, whereas in other places the glands were distended by mucin containing signet ring cells, and seperated by loose connective tissue infiltrated by plasma cells, lymphocytes and a few polymorphonuclear leucocytes. (fig. 3,*D*).

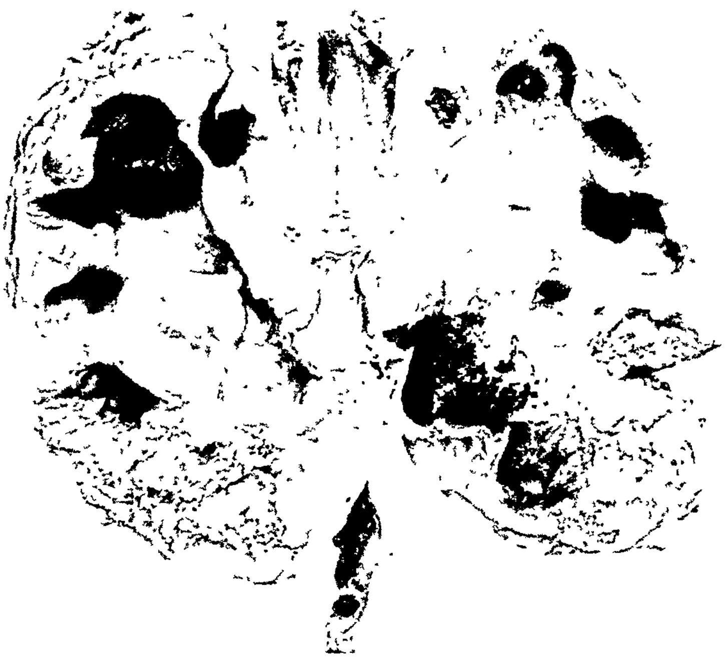

FIG. 2. Gross specimen, showing gelatinous-like tumor mass of lower minor calyx infiltrating into adjacent fibrotic medullary and cortical tissue.

In the deeper portion of the section, the parenchyma of the medulla was replaced by loose connective tissue heavily infiltrated by lymphocytes, plasma cells, and a few polymorphonuclear leukocytes. Here and there dilated, degenerating, collecting tubules were seen, and in places where the inflammatory changes were severe there were numerous nests of pseudoxanthoma cells (fig. 4,*A*).

The cortex of the kidney in this area was transformed into a dense fibrous connective tissue stroma infiltrated by round cells. Single atrophic glomeruli with thickened Bowman's capsule and atropic convoluted tubules were still discernible (fig. 4,*B*).

In addition to the inflammatory changes noted in the medulla and cortex of the kidney, characteristic of an old chronic ascending pyelonephritis, the tissue was also invaded by nests of tumor tissue similar to that described lining the inferior minor calyx of the kidney (*fig. 5*).

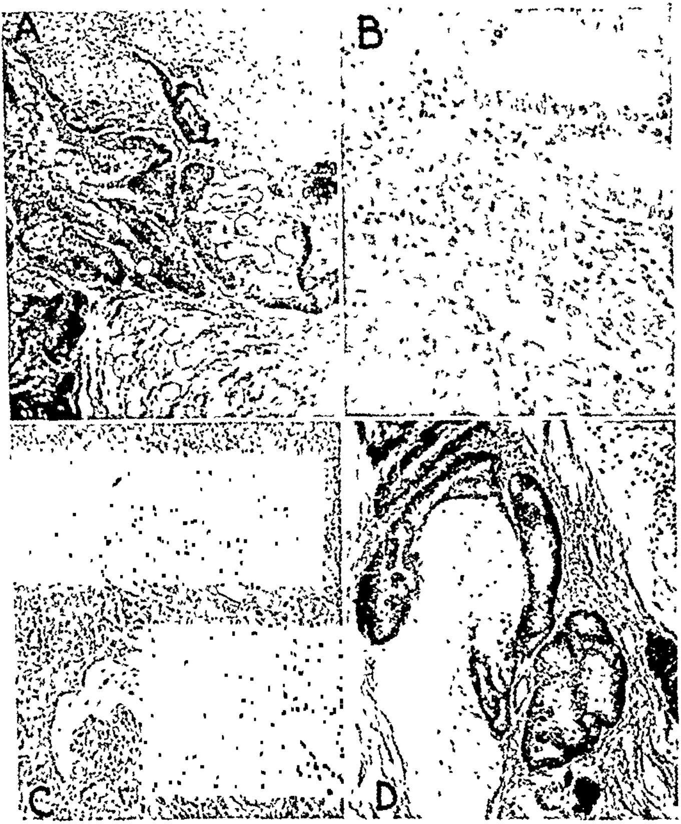

Fig 3 *A*, tumor mass of minor calyx, showing glands lined by cuboidal and columnar cells Hemalum and eosin stain. × 100. *B*, infiltrating tumor acini, showing mitotic figures. Hemalum and eosin stain. × 320. *C*, showing tall columnar cells with goblets of mucin in cytoplasm Hemalum and eosin stain. × 160. *D*, distended glands, showing much mucin and few signet ring cells Hemalum and eosin stain. × 100.

The diagnosis was mucus producing adenocarcinoma associated with a chronic ascending pyelonephritis and nephrolithiasis.

About 10 months after the first admission the patient was readmitted with complaints of injury to the back incurred in a fall 5 months prior to re-admission. Since that time she had been suffering pain in the thoraco-lumbar area. Associated with her pain was a rather marked weight loss and weakness. Physical examination revealed slight tremor of the tongue; heart enlarged to the left and a systolic murmer at the apex. The heart rate was 100 times per minute. The rhythm was normal. A few wheezing rales were heard in the middle and

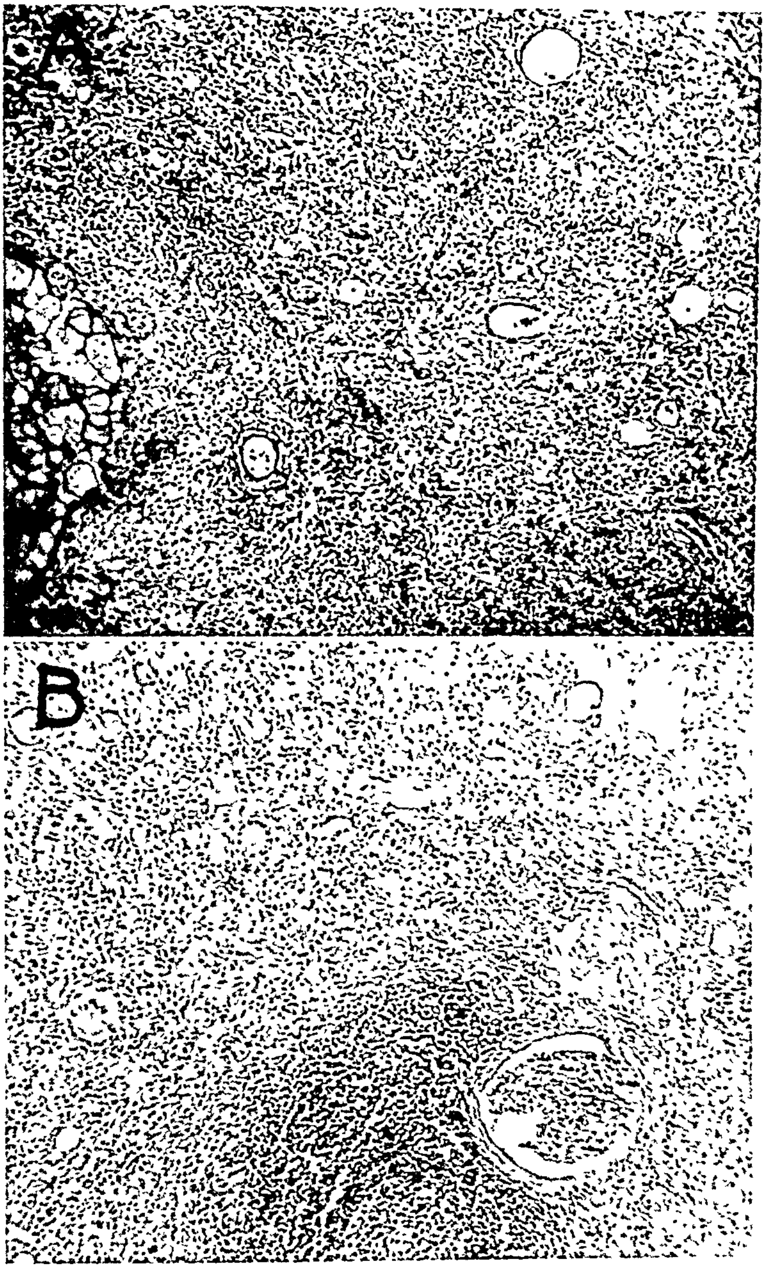

FIG. 4. *A*, renal parenchyma displaced by marked inflammatory exudate containing xanthoma cells. Note small metastasis in medulla. Hemalum and eosin stain. × 100. *B*, marked pyelonephritic change with atrophy of glomerulus and fibrosis of Bowman's capsule. Hemalum and eosin stain. × 100.

lower chest posteriorly. The abdomen was obese, and tenderness was elicited in the right upper quadrant and over the right lumbar region. Neurological examination revealed normal reflexes, but a definite weakness of the left side, as characterized by weakness of the left grip, some weakness on flexion, and more so on extension of the left extremities. Deviation of the tongue to the right was noted on protusion. The fundi were normal, and tenderness was elicited over the 4th and 5th thoracic vertebrae and over the lumbar spine.

An x-ray of the chest on November 14, 1940 revealed an increase in the right hilus, and extending from the hilus were rounded areas of increased densities with infiltration and extension into the right base. Suggestion of fluid in the right costophrenic angle was also noted. A second x-ray taken 2 weeks later showed a more marked infiltration throughout both lung fields with thickening of the right pleura. An x-ray of the skull and pelvis failed to reveal any evidence of metastases.

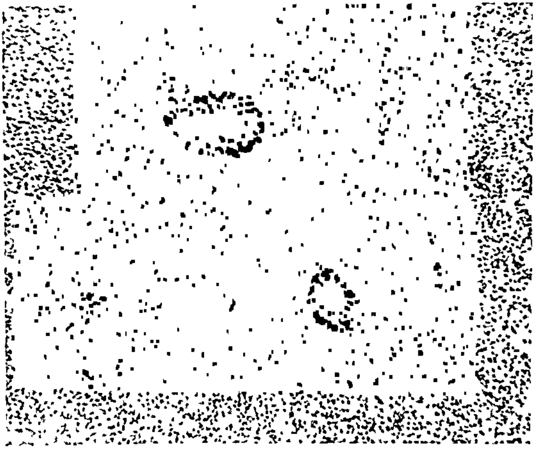

FIG. 5. Tumor nests infiltrating cortex of kidney. Hemalum and eosin stain. × 100.

The red blood cell count was 3,500,000, white blood cells 9,400. The blood chemistry was normal. The basal metabolism rate was plus 15. The spinal fluid chlorides were 670, and the total proteins were 70 mg./100 cc.

An electrocardiogram showed evidence of myocardial damage. The patient failed to improve and began to show obvious signs of cardiac decompensation, and died 1 month after the last admission to the hospital. Permission to perform an autopsy was refused.

DISCUSSION

Aside from the fact that the presence of a mucus producing adenocarcinoma of the renal pelvis is rare, this being the third case reported, there are a number of interesting features to be considered that present themselves in the pathogenesis of glandular structures of the mucosa of the renal pelvis.

It is a well known fact that metaplasia of transitional epithelium to squamous epithelium occurs in inflammations of the renal pelvis, ureter, urinary bladder, and the upper portion of the urethra. Irritation or infection as a provocation of metaplasia of the columnar epithelium to squamous epithelium is also of common occurrence, as noted in such organs as the cervix, pulmonary bronchi, and nasopharynx (polyps). However, metaplasia of transitional cell epithelium to columnar epithelium with glandular formation (pyelitis cystica or cystitis glandularis) is of rather uncommon occurrence and seems to be limited to the kidney-urinary bladder tract system.

This observation was first made in the urinary bladder by Stoerck[6] in 1899 and later by Stoerck and Zuckerkandel[7]. Brütt[8], in 1923, first described pyelitis glandularis associated with a pyonephritic atrophy of the kidney. Since then single cases have been reported by Pashkis[9] and Foot.[10] In the latter's case, the kidney was removed for pyonephrosis with renal calculus of long standing; mucus producing glands in the pelvis of the kidney were demonstrated histologically.

It seems to be generally agreed that metaplasia of transitional cell epithelium to cylindrical epithelium forming glands in the kidney pelvis and urinary bladder tract may occur.[7, 10, 11, 12, 13, 14] However, the mechanism involved in this process of metaplasia is interpreted differently by different investigators. Foot[10] believes that cystitis glandularis should not be confused with the far more common lesion of cystitis cystica or follicularis, which he believes is not a metaplasia of transitional cell epithelium. On the other hand, Ewing[11] points out that in cystitis cystica many of the invaginated epithelial nests or tubules are lined by cylindrical cells and these modified cells develop secretory tendencies. Stoerck[6] has traced a definite relationship between cystitis cystica and its forerunner, cystitis granulosa, with multiple papillomas of the urinary bladder. Craig,[12] Paschkis[9] and Patch and Rhea[13] are also of the opinion that cystitis glandularis may develop in a process of metaplasia through different stages from cell nests of Brünn to cystitis cystica and subsequently to cystitis glandularis. Patch and Rhea[13] also support the contention that cysts which develop in epithelial nests of Brünn are the results of an actively secreting process rather than a degenera-

[6] Stoerk, O.: Beitrage zur Pathologie der Schleimhaut, der Harnleitenden Wege. Beit. zur path. Anat. u.z. allg. Path. **26**: 367, 1899.

[7] Stoerk, O. and Zuckerkandl, O.: Über Cystitis Glandularis und den Drüsen-Krebs der Harnblasse. Ztschr. f. Urol. **1**: 1, 1907.

[8] Brütt, H.: Über Pyelitis Glandularis. Ztschr. f. urol. Chir., **14**: 157, 1923–24.

[9] Paschkis, R.: Beitrage zur Pathologie des Nierenbeckens, Folio Urologica, **17**: 55, 1912–13.

[10] Foot, N. C.: Glandular metaplasia of the epithelium of the urinary tract. South. Med. J. **37**: 137, 1944.

[11] Saphir, O. and Kurland, S. K.: Adenocarcinoma of the urinary bladder. Urol. & Cutan. Rev., **43**: 709, 1939.

[12] Craig, L. J.: Cystitis cystica glandularis. J. Urol. **42**: 1197, 1939.

[13] Patch, F. S. and Rhea, L. J.: The genesis and development of Brunn's nests and their relation to cystitis cystica, cystitis glandularis and primary adenocarcinoma of the bladder. Canad. Med. Assoc. J., **33**: 597, 1935.

[14] Ewing, J.: Neoplastic Diseases, Philadelphia: W. B. Saunders Co., 1940, p. 941. 4th ed.

tive one, and that these cysts may develop into glandular formations lined by tall epithelial cells that can acquire the property of secreting mucus

Giani,[15] working with laboratory animals, was able to produce experimentally, by inserting celloidin tubes as an irritating factor, a cystitis granulosa and a cystitis cystica He concludes that any cause which during a certain period of time stimulates epithelial cells to a more active proliferation can lead to the development of Brunn's nests and cystitis cystica

We likewise, in our examination of biopsies and sections of the kidney pelvis, and urinary bladder tract, have found these different stages of cystitis granularis and cystitis cystica and occasionally cystitis glandularis Not infrequently we were also able to demonstrate that the inner layer of cells lining the cystic structure of Brunn's nests were of cylindrical epithelium

Craig,[12] Paschkis,[9] and Eisendrath and Rolnick[16] are of the opinion that cystitis glandularis is potentially, not actually, malignant, but may be a point of origin for adenocarcinoma of the urinary bladder

Tumors (adenocarcinomas) arising in the urinary bladder from a pre existing cystitis glandularis must be differentiated from those arising in the dome or in the trigone of the urinary bladder, as emphasized by Stirling and Ash,[17] Saphir,[12] and Foot

Normally, glands have never been described in a normal pelvis mucosa of the kidney (Maximow and Bloom)[18] and Pashkis [14] The formation of glandular lesions, such as a pyelitis glandularis or a mucus producing adenocarcinoma, must be attributed to a metaplasia of the transitional cell epithelium to these gland-like structures following previous inflammatory changes or mechanical irritation that may be produced by renal calculi This point of view is upheld by Brutt, Pashkis, and Foot [10]

It is also apparent, in our case, that the mucus producing adenocarcinoma developed secondarily to severe pyonephrosis, ascending pyelonephritis, and a staghorn stone of the pelvis and calyces that had been present for some time before the onset of the malignant growth, which was shown to infiltrate the pyelonephritic inflammatory stroma

SUMMARY

A case of mucus producing adenocarcinoma of the renal pelvis is presented It is the third case in the literature The pathogenesis is based on pre existing pyonephrosis and ascending pyelonephritis and staghorn stone which most likely stimulated the mucosa of the pelvis to undergo a metaplasia to that of a pyelitis granulosa, pyelitis cystica, pyelitis glandularis, and finally to that of a mucus producing adenocarcinoma

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[15] Giani, R Neuer Experimenteller Beitrag zur Entstehung der Cystitis Cystica Beit path Anat und allg Path 42 1, 1907

[16] Eisendrath, D N and Rolnick, H C Urology Philadelphia J B Lippincott Co 1938, p 468, 4th ed

[17] Stirling, C and Ash, J E Chronic proliferative lesions of the urinary tract J Urol 45. 342, 1941

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ANEURYSM OF THE RENAL ARTERY

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In the most recent review of the literature, 86 cases of aneurysm of the renal artery have been collected. Several excellent surveys of this subject have been made in the past few years. This will not be repeated here. It is desired, however, to point out that in more than half of the reported cases, trauma is considered to be the etiological agent. Wesson emphasizes the point that trauma to the renal pedicle with spontaneous arrest of hemorrhage by encapsulation and possibly later calcification in the hematoma, should not be classified as a renal aneurysm. This should not be dismissed as hair-splitting or puritanism, but is in fact a plea for greater scientific accuracy. Re-examining the literature from this point of view and deleting the traumatic "false" aneurysms, there appear to be only 40 "true" aneurysms (including the case presented here).

CASE REPORT

J. R. N., a 46 year old white man, was admitted to the medical service of this hospital in November 1947, complaining of headache, vomiting and pain in the left chest.

The duration of his symptoms was about 6 weeks. In addition, he had had shortness of breath and palpitation on exertion for several years. He had been aware of no urinary symptoms, except for some recent increase in diurnal and nocturnal frequency. During the past 11 years, he had been treated in various mental hospitals for hebephrenic schizophrenia. His past history was otherwise not contributory.

The patient appeared to be well developed and well nourished, and did not appear ill. An elevated blood pressure (242/150), moderate cardiac enlargement to the left, and questionable tenderness in the left hypochondrium and in both costovertebral angles, were the only significant findings.

Urinalysis on admission, and all later specimens, showed 2 to 4 plus albumin and occasional granular casts. Urinary concentration appeared adequate. Blood counts and blood chemistries were within normal limits. The Kahn test was negative. Sedimentation rate was elevated. Urea clearance was only 56 per cent of average normal. X-ray of chest showed no abnormality. Excretory urogram (fig. 1, *A* and *B*) showed fairly prompt and equal output of contrast medium. The presence of a right renal calculus was reported. Gallbladder studies showed normal visulaization (fig. 1, *C*). Electrocardiogram showed left axis deviation and minor changes consistent with left ventricular strain. A gastrocnemius muscle biopsy showed no pathological changes.

Cystoscopic examination added no further information. Retrograde studies showed the calcification to be medial to the upper pole of the right kidney and apparently outside the kidney. Perirenal air insufflation (fig. 1, *D*) contributed little diagnostic information. Aortography was considered too hazardous in this

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HEMATURIA AND SICKLE CELL DISEASE· UNEXPLAINED, GROSS UNILATERAL, RENAL HEMATURIA IN NEGROES, COINCIDENT WITH THE BLOOD SICKLING TRAIT

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"Idiopathic" or "essential" hematuria is probably due to a number of causes It is only with time and advancement of knowledge that we shall be able to identify the pathogenesis in at least some cases of hematuria of undetermined origin

We have observed 4 cases of unexplained unilateral renal hematuria associated with the blood sickling trait in Negroes The affected kidney from each of two of these cases was available for pathologic examination one following nephrectomy, and the other from autopsy The other 2 cases have been the subjects of exhaustive clinical studies No recognized cause of hematuria has been found in any of these cases In addition, a search of the hospital records of unexplained hematuria in Negroes has unearthed three additional cases of "essential" hematuria co-incident with the blood sickling trait, which may or may not belong with the above group

At present, we cannot say whether or not any of these, or other cases of unexplained renal hematuria in Negroes, are related to the sickling trait The following reports (summarized in table 1) suggest some relationship, particularly when considered in terms of the already described clinical pathology of sickle cell anemia where widespread small infarctions are present Since we have been unable to find reference to similar observations in the literature,[2] we believe that it is important to suggest this possibility in order to stimulate search for further causes which will substantiate or rule out a causal relationship

CASE REPORTS

Case 1 C Y (B G H No 12639), a 19 year old Negro soldier, was admitted to the Brooke General Hospital on June 15, 1946 because of severe hematuria of unknown cause, which had persisted for several months The patient gave a history of recurrent attacks of joint pain accompanied by weakness and fatigue at two to four month intervals since childhood He had suffered gross hematuria for at least a month before May 10, 1946, when he was admitted to the 124th Evacuation Hospital overseas At times the hemorrhage had been brisk At other times it caused only a haziness of the urine Because of the persistent hematuria, he was transferred to Camp Kilmer, New Jersey, where a careful urological study indicated that the source of bleeding was the left upper urinary tract

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[1] National Research Council Fellow in the Medical Sciences

[2] While this paper was in manuscript form, we were interested to find a report of a similar case by Abel and Brown in the February 28, 1948 J A M A Their case seems to be in the same category as our cases, and the symptoms described are strikingly similar to our case 4

TABLE I

CASE	AGE	SEX	SITE OF HEMATURIA	DURATION	BLOOD SICKLING	SICKLE CELL ANEMIA	PATH. FINDINGS	OUTCOME
1. BGH No. 12639	19	M	Left kidney	3 mos.	"Marked"	Yes, severe	Figs. 1–2	Left nephrectomy
2. JHH No. 196848	34	M	Rt. kidney	3½ mos.	Seen in Path. slides; no ante mortem diagnosis	Questionable; probably trait only	Figs. 3–5	Expl. rt. kidney Died suddenly 14 days P.O.; autopsy
3. JHH No. A47300	11	M	Left kidney	3 years	95% in 7 hrs.	Mild anemia; ? trait only or sickle cell anemia	No specimen	Conservative treatment living and "well."
4. JHH No. 127341	23	F	Rt. kidney (since June 1946) ? Lt. kidney in January 1945.	3½ years	Variable 95–100% 12 hrs.	Yes, severe Life-long	No specimen	Conservative treatment Living and "well." Pregnant second time.
5. JHH No. 143079	44	F	Uncertain; probably rt. kidney	3 episodes 1937 to 1941	35% in 24 hrs.	Trait only	No specimen	Not followed or treated
6. JHH No. 124139	34	M	? bilateral; definitely, left	6 wks.	Begins 4 hrs. Complete 19 hrs.	? Trait only	No specimen	Not followed; hematuria ceased with vitamin C treatment.
7. JHH No. 151235	41	F	Undetermined	3–4 days acute P.O.	Seen in Path. slide of uterus	? Trait only	No kidney specimen	Not followed or treated.

No demonstrable lesion was present Smears and cultures of the urine were negative for tuberculosis He was then transferred to the Brooke General Hospital, where further study was undertaken

Physical examination was normal except for marked weakness

Laboratory studies red blood cell count, 2 million per cu mm , icteric index, not recorded, sickling preparation, "very marked sickling trait", urine loaded with red blood cells, rare white blood cells, no casts, urobilin not recorded, Wassermann was not recorded X rays of the chest and skeleton were normal

Intravenous urograms showed a normal right upper urinary tract The left renal pelvis and calyces were incompletely outlined, suggesting many filling defects Cystoscopy confirmed the left upper tract as the source of the bleeding A left retrograde pyelogram revealed the same findings as those of the intravenous urogram Aspiration of the contents of the left renal pelvis through an ureteral catheter produced only blood

The patient was treated conservatively with transfusions and rest for nearly a month The hematuria persisted, however On July 11, 1946 (about 3 months after the onset of hematuria) a left nephrectomy was performed The indications were risk of exsanguination and the high incidence of severe blood transfusion reaction in cases of sickle cell anemia The postoperative course was uneventful Hematuria ceased, and the anemia improved slightly for the duration of observation

Pathologic examination The kidney measured 9 by 5 cm The outer surface was smooth, grayish blue, and glistening The capsule stripped with slight difficulty The cut surface was quite congested The cortex was 4 mm in thickness The medullary pyramids appeared to be somewhat swollen Several of the papillae showed gross evidence of superficial erosion of the mucosa, associated with reddish purple discoloration The mucosa of the calyces and pelvis was injected There was nothing to suggest tumor, tuberculosis, or other cause of hematuria

Numerous sections were taken for microscopic examination Sections through the papillae showed some erosion of the lining epithelium, but for the most part, this appeared to be an artefact In some areas the surface was partially denuded of epithelium The underlying stroma showed moderate infiltration and fibrosis It was thought that the absence of lining epithelium in these areas might be pathological A striking feature of the papillae was the presence of numerous greatly dilated capillaries and venules just beneath the epithelium There were some vessels filled with red cells exhibiting many bizarre shapes, obviously sickle cells Sections from the cortex did not appear to be particularly significant Figures 1 and 2 show the important findings in this case

Experience with this case reminded one of us of another Negro with a similar history of unexplained unilateral renal hematuria observed several years previously The records in his case were reviewed and proved to be of considerable interest

Case 2 H B (J H H No. 196848, autopsy No 17001), a 34 year old Negro, was admitted to the medical service of The Johns Hopkins Hospital on March

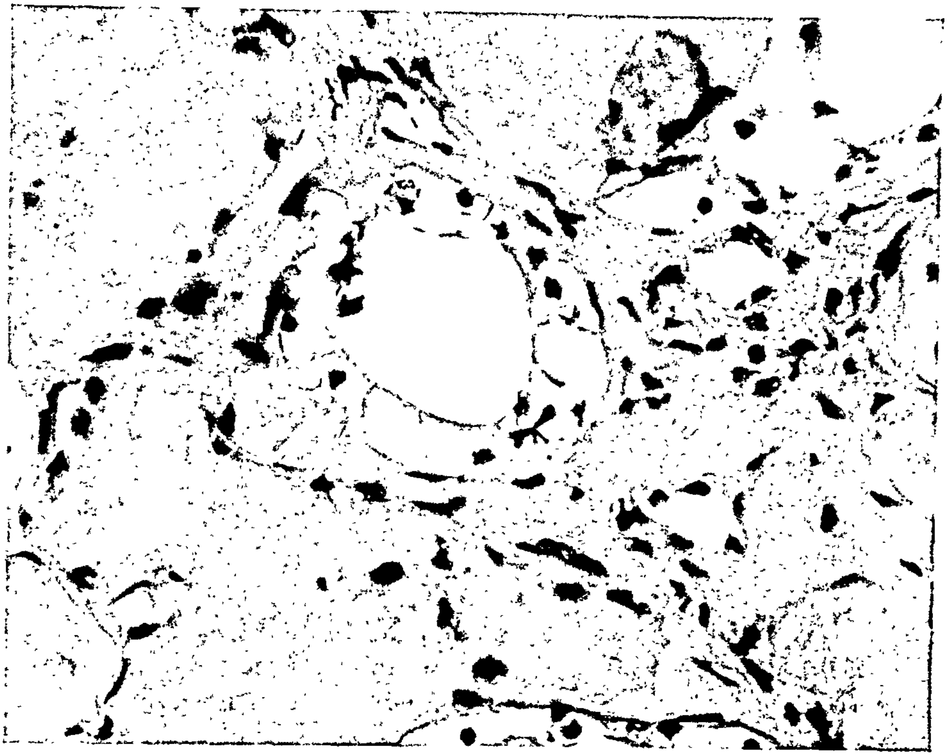

FIG. 1. Case 1. Dilated peritubular sinuses. × 500

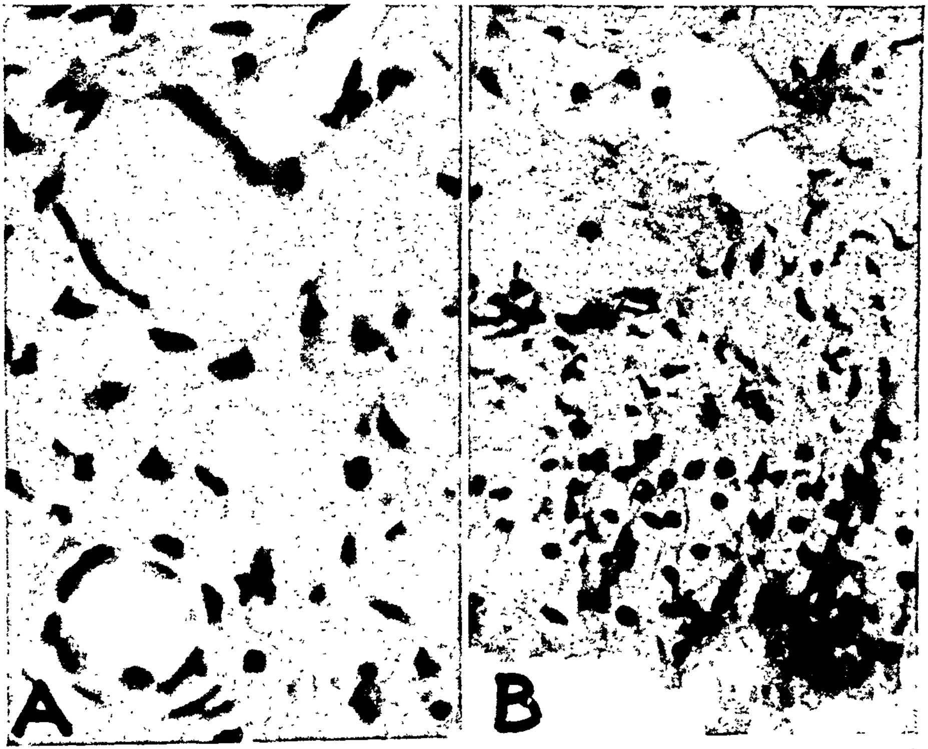

Fig. 2. Case 1. *A*, rupture of small, thin-walled vein in papilla with extravasation of blood into interstitial tissue. × 800. *B*, hemorrhage in intersitital tissue beneath pelvic epithelium. × 500.

28, 1940 because of dyspnea and hematuria He was later readmitted to the urological service on July 2, 1940 because of severe unexplained hematuria

On the medical admission he gave a history of repeated attacks of dyspnea, orthopnea, ankle edema, cough, weight loss, palpitation and weakness of 3 months' duration He denied chills and fever and gave no history of rheumatic fever He had never noted hematuria previously However, the complete dispensary history and examination by Dr W Halsey Barker the day before admission revealed "red amber" urine which contained 30–40 red blood cells per high power field uncentrifuged A part of Dr Barker's impression reads as follows "The signs are characteristic of aortic stenosis, without marked widening of the aorta as observed at fluoroscopy This is probably rheumatic in origin, although there is no history to substantiate it There is also mitral insufficiency and evidence of cardiac failure, which is chiefly asymptomatic The striking hematuria is puzzling This may be the result of a renal infarct Nephritis seems unlikely with no casts present "

Physical examination revealed an orthopneic, undernourished Negro, who coughed frequently He had a fever of 102 F, a pulse rate of 106 per minute, respiratory rate of 30 per minute, and a blood pressure of 98/70 mm Hg The lower lung fields were dull to percussion The heart was enlarged and the rhythm was rapid and regular There was a harsh systolic murmur over the precordium. Abdominal examination was not remarkable The neurological examination was normal

Laboratory studies red blood cell count, 4 9 million per cu mm , hemoglobin 12 gm per cent, white blood cell count 6400 per cu mm , normal blood smear, normal platelet count, icteric index from 5 to 7 5 No sickling preparations were made The serological test for syphilis was positive The urine contained some albumin, a few white blood cells and many red blood cells The urine was 1 plus positive for urobilin on admission During the whole admission the hematuria varied in severity from 5 to innumerable red blood cells per high power field even after the heart became well compensated On many occasions the urine was grossly bloody There were no casts Urine cultures were sterile Sputum and urine cultures were negative for tuberculosis A chest x ray showed no abnormality other than the enlarged heart Intravenous urograms showed functioning kidneys on each side with no sign of stone or filling defect

Treatment consisted of digitalis and rest He responded well The hematuria persisted with exacerbation Because of this he was seen in urological consultation Cystoscopy on April 25 was not remarkable except that a urethral stricture was discovered A left retrograde pyelogram was normal There was no demonstrable abnormality of the urinary tract save for unexplained hematuria

He was discharged after a month to be followed in the urological dispensary for the hematuria from May 8 to July 2, 1940 Cystoscopy was repeated on June 11 Gross blood was seen coming from the right ureteral orifice A right retrograde pyelogram was interpreted as "stereo right pyelogram shows an apparent filling defect in the lower major calyx of the right kidney suggesting strongly a clot, non opaque stone or tumor "

An attempt was made to control the right renal hematuria with x-ray therapy for aproximately 2 weeks without effect.

On July 2, 1940 he was admitted to the Brady Urological Institute for exploration of the right kidney to rule out tumor as the cause of bleeding. Examination showed the cardiovascular system to be fairly well compensated. His heart was still enlarged. There was a forceful apical beat. The blood pressure was 75/50 mm.Hg. Abdominal examination was normal. The spleen was not felt. The lower pole of the right kidney seemed to be palpable to some observers. The blood hemoglobin wa 12 gm. per cent, and the urine on this second admission was still grossly bloody, as it had been on every observation in the urological dispensary.

The right kidney was explored on July 8, 1940, by Dr. Henry Harrill. In part, the operative note read as follows: "The kidney and ureter were mobilized and exposed. Palpation of the kidney, ureter and pelvis showed no thickening or other external evidence of tumor. An incision 1.5 cm. long was made in the renal pelvis. With retractors and a good light the inside of the pelvis was visualized very well. The papillae were seen in the upper and middle calyces, and they appeared to be perfectly normal except for congestion. The mucous membrane of the pelvis itself was also congested. Here and there were patches of excoriated hemorrhagic areas of variable size which bled easily on the least provocation. It was then quite certain that no tumor was present and that the probable sites of bleeding were the hemorrhagic areas seen in the pelvis. The pelvis was irrigated with one-half per cent silver nitrate and the kidney replaced in normal position."

On the day of operation the patient's condition was good. A postoperative urine specimen contained no blood. Subsequently he developed dyspnea, rapid pulse, temperature of 102 F and rales at the left base. He was given intravenous fluids, and sulfathiazole was begun on the third post operative day. On the fourteenth postoperative day, without warning, his pulse suddenly became thready, weak and rapid. The temperature rose from normal to 103 F. He died shortly thereafter, presumably in cardiac failure. His white blood cell count had remained normal during this period.

Autopsy: The gross pathologic findings were: right pyelotomy; granular calculi (acetyl sulfathiazole) in the right renal pelvis; hemorrhagic pyelitis on the right; fused calcified aortic cusps with extreme stenosis and insufficiency; cardiac hypertrophy; chronic passive congestion of the viscera; and chronic cystitis.

At no time during the hospitalization of this patient, or in the succeeding initial pathologic examination, was the possibility of sickling phenomena mentioned. We were prompted by the experience with case 1, and our almost simultaneous observation of case 3, to review the slides of the old autopsy done 7 years before.

Microscopic examination: typical sickle cell forms were found in the vessels of the spleen and kidneys (fig. 3). The spleen showed some of the pathologic changes which Rich (1938) has described as typical of sicklemia. The capsule was slightly thickened. The sinusoids were greatly congested; and pools of blood were observed in the pulp.

Grossly the right kidney showed purplish discoloration of some of the papillae of the pyramids, which appeared to be filled with blood. In the minor calyces and the pelvis were small accumulations of hard, yellow granules of sulfathiazole. The pelvic mucosa exhibited numerous hemorrhagic points, which were confluent in some areas. Microscopically, the glomeruli of the kidney were essentially normal. The tubules exhibited brown granular pigment in some of the epithelial cells.

This pigment gave the Prussian blue reaction for iron. The interstitial tissue showed some areas of recent and organized hemorrhage, particularly near the papillae. Some of the papillae showed many areas of marked engorgement of small blood vessels. Some of these were very close to the mucosal surface and were filled with sickle cells (figs. 4 and 5). The left, non-bleeding kidney showed some of the same engorgement of vessels, presumably due to passive congestion. The changes were not as great as on the right side however.

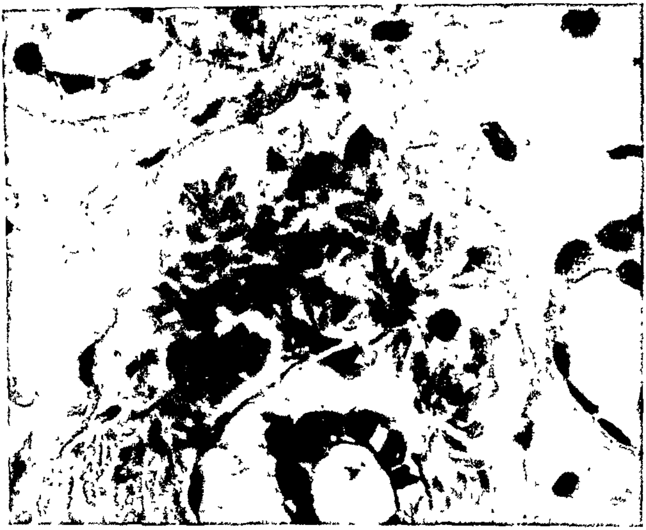

FIG. 3. Case 2. Sickled cells in dilated peritubular venous sinus. × 800

It is evident from the history that the patient had intermittent, gross hematuria for at least 3 month before he died. He was given sulfathiazole *only from* the third to the fourteenth postoperative day and had been bleeding from his *right kidney long before this. We believe that the sulfathiazole crystals found* in the right renal pelvis at autopsy did not contribute to the hematuria. After careful examination of the kidney, we felt that the hyperemic areas in the papillae, as described above, were the only possible sources of bleeding demonstrable in these sections.

At the time these 2 cases came to our attention, case 3 with a strikingly comparable history was being followed by one of us in the Johns Hopkins Hospital.

Case 3. C. W. (J.H.H. No. A47300), an 11 year old Negro, was admitted to the Harriet Lane Home by Dr. Frank W. Kibbe for the first time on April 2, 1946 with the chief complaint of bloody urine. Family and past history were noncontributory. In the Spring of 1945 the child was struck in the left flank by a baseball. Following this he had the first episode of bloody urine, which lasted about a week. From then until April 1946 at least one other attack of painless hematuria occurred without any trauma. The attack which led to admission was without history of trauma or pain. Bloody urine was noted by both the mother

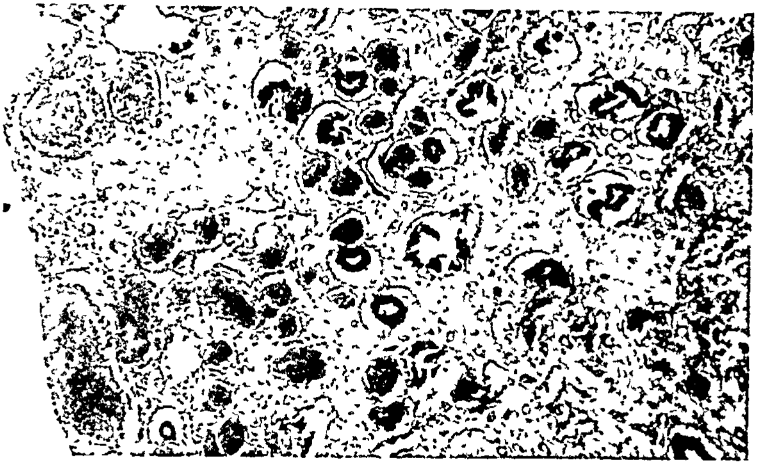

FIG. 4. Case 2. Dilated veins in papilla. × 50

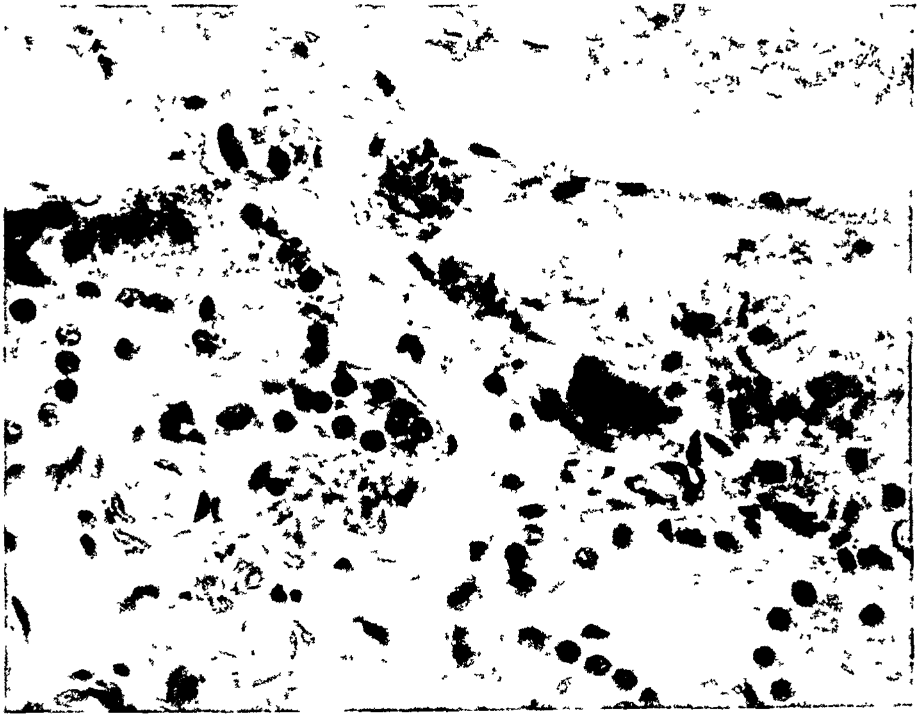

FIG 5 Case 2 Detail of dilated veins in papilla near pelvic epithelium. Note destruction of vascular walls in some areas. × 500

and the patient The family physician prescribed "some pills" When the hematuria did not clear up, the child was brought to the hospital where he was admitted The parents denied any history of throat infection, swelling, swelling of the legs, shortness of breath, joint pains, or nosebleeds in the patient No medication had been taken before the bleeding started

Physical examination revealed an apparently normal though unusually pale child There was no jaundice The spleen was not felt There was no evidence of hemorrhage or petechiae in the skin There was a moderate phimosis The rest of the examination was not remarkable

Laboratory studies red blood cell count, 3 9 million per cu mm , hemoglobin, 10 2 gm per cent, normal blood smear, normal platelet count, icteric index not done, wet sickling preparation, 3 hrs , occasional sickling, and 7 hours 95 per cent sickling Urine grossly bloody in three glasses, microscopic no casts and only a rare white blood cell, but loaded with red blood cells, specific gravity, 1 024, *p*H, 6 0, albumen, 3 plus, sugar, 0, urobilin, 0 Urine cultures were sterile The dilution—concentration test, phenolsulphonphthalein test, blood nonprotein nitrogen, total blood proteins, and the serum albumin globulin ratio were all normal The serological test for syphilis was negative

When he was seen in urological consultation, careful studies were all normal These included two intravenous urograms and cystoscopy at a time when he was not bleeding A few days later, when his urine was found to be grossly bloody, cystoscopy was repeated On this occasion dark, bloody urine was seen spurting from the left ureteral orifice Clear urine spurted from the right ureteral orifice A left retrograde pyelogram appeared normal

The blood hemoglobin dropped to 5 7 gm per cent on May 8 He was treated conservatively with bed rest, iron and large doses of vitamin C Gradually the gross hematuria subsided At the time of discharge on May 15, 1946 there were only rare red blood cells to be found in the microscopic examination of the urine The blood hemoglobin at the time of discharge was only 8 gm per cent

On January 7, 1948 he was again seen in urological consultation because of a recurrence of hematuria The history and findings were almost exactly the same as they had been in April and May of 1946 The previous studies were repeated All were normal save the observation of gross bleeding from the left ureteral orifice The bloody urine collected from the left side by ureteral catheter showed many, bizarre sickle cell forms Urine culture studies, including those for tuberculosis, were again negative The intravenous and left retrograde pyelograms were again normal His hemoglobin at this time was 13 5 gm per cent No icteric index was reported, but there was no evidence of jaundice The child gained 6 pounds in the past year and appeared in good health, except for his complaint

Conservative treatment was again elected When last seen on January 15, the urine was microscopically clear and negative, and he had no further complaints He is to be followed with intravenous urograms every 6 months for two more years

With the experience gained from the first 3 cases and the one to follow, the case is classified as "hematuria (left renal) of unexplained etiology, co existing with the sickle cell trait." The time interval since the onset (1945) and the negative urograms seem to preclude the common and usually recognized causes of hematuria. The unilateral character of the disease rules out the common nephritides. We believe that the patient will most certainly best be treated conservatively and that there is some connection between his hematuria and his sicklemia.

The fourth case we found as a direct consequence of our knowledge of the first three and a search through the hospital records for gross hematuria associated with sickling. Dr. Douglas Carroll of the Department of Medicine called this one to our attention as he was reviewing the cases of sickle cell anemia for other purposes. This is the most interesting of all these cases, as she has been followed constantly in the Johns Hopkins Hospital since her birth here in 1924. Her records are voluminous. She was studied in Dr. M. M. Wintrobe's Hematology Clinic from 1938 to 1944, and she is the only one of these patients upon whom hematology studies are adequate enough to justify the unquestionable diagnosis of sickle cell anemia—as opposed to the sickling trait alone without the usual stigmata of the anemia.

Case 4. D.S. (J.H.H No 127304) was a 23 year old Negress who was admitted to the hospital for the fourteenth time in December 1947. Six of the fourteen admissions had been because of hematuria in some degree. She had been known to have sickle cell anemia since 1928.

Prominent in her history are the complaints of severe and recurrent epistaxis and "cystitis." She first suffered with cystitis in October 1929, at which time white cells but no red cells were found in her urine. At the time of a surgical admission for appendectomy in July 1938, her urine was said to be normal. In July 1944 when she was treated for primary syphilis with penicillin, her urine was "negative." However, she was seen in the gynecological out-patient department in August of 1944 because of hematuria. This was thought to be caused by "hemorrhagic cystitis," but the cystoscopic note describes an essentially normal bladder. This was the first record of many episodes of prolonged severe hematuria.

The notes in her history concerning her almost uncontrollable epistaxis are impressive. The first severe episode was in 1937. Since that time she has been seen by the nose and throat staff two or three times a year for intractable nosebleeds. These have been always more than usually difficult to control. Some observers described "ulcerated areas" in the nasal mucosa. The repeated severe nosebleeds were never correlated with her sickling disease, although Wintrobe (1946) specifically states that epistaxis is a frequent complaint in sicklemia.

In the Hematology Clinic the case was considered to be a typical example of sickle cell disease. She had a chronically low hemoglobin and red blood cell count, with marked sickling, all subject to considerable variations. Her red blood cell count was 3.3 million per cu. mm., and her blood hemoglobin was 8.4 gm. per cent. The icteric index varied from 5 to 20 when she was in crisis. Blood bilirubin was 1.8 mg. per cent total with a direct of 0.8 mg. per cent. Her urine was negative for urobilin on several occasions. X-rays of her bones showed some changes in density but no deformity typical of sickle cell disease.

Her mother and brother were found to have the sickle trait without anemia. Other members of the family did not have it.

She was admitted to the obstetrical service in January 1945, because of "vaginal" hemorrhage. It was thought that this bleeding was related to her first pregnancy at that time. Careful obstetrical examination failed to reveal any cervical bleeding. One urine specimen was reported as negative. (In light of subsequent developments, one wonders if the "vaginal" bleeding was not coming from her urinary tract.) She was again admitted the next month with the same complaint of "vaginal bleeding." In addition she suffered from tenderness in the left costovertebral angle and pain radiating to her pubis. She also had joint pain at this time. A thorough study revealed that the bleeding originated in the urinary and not the genital tract. The sterile urine was grossly bloody and filled with clots. After 5 days, gross hematuria subsided. Air cystoscopy disclosed no source of the bleeding. Because of suggestive left ureteral colic, x-rays were made but showed no stones. She had pains in the arm, leg and joints, which were attributed to an exacerbation of her sickle cell anemia. Treatment was administration of transfusions and vitamin K.

In March 1945, she was delivered of a healthy male child. Three days postpartum she complained of severe bilateral lower quadrant pain. Two days later her urine contained 10-15 red blood cells per high power field.

She was next seen in the accident room in June 1946 when she complained of pains in the right side. There was extreme abdominal tenderness. It was thought that she might have either an ectopic pregnancy or an ureteral calculus. X-ray revealed no sign of stone. She returned for a second time in July, with the complaint of gross hematuria and passage of blood clots. The impression of the examiner was "sickle cell anemia crisis; ? hemorrhagic cystitis." When she was seen the next day in the gynecological out patient clinic, she had severe right lower quadrant pain, nausea and vomiting. Her blood hemoglobin was 7.5 gm. per cent. A sickling preparation showed "4 plus" sickling. Urine culture showed Aerobacter aerogenes. Differential phenolsulphonphthalein test showed some decrease of function on the right side. Studies for tuberculosis were negative. A right retrograde pyelogram was "normal."

It was at this time that we became interested in her case. She refused to come into the hospital for study, however, until January 1947, when she had another extremely painful episode almost exactly like the above and was admitted by way of the accident room.

One of us was fortunate enough to see her at this time, when she was acutely ill. We were impressed with the findings which seemed closely to parallel the preceding three cases. She was in great pain and presented the typical picture of right ureteral colic. The impression was that she was bleeding from her right kidney and that the passage of blood clots was causing the symptoms. An intravenous urogram was not remarkable except for some filling defects in the right renal pelvis, suggestive of clots. Immediate water cystoscopy revealed a bladder filled with clots and dark, bloody urine. After thorough washing, the bladder appeared normal except that dark, bloody urine and a few clots were seen to spurt from the right ureteral orifice. The urine from the left side was clear. A No. 6 ureteral catheter was passed to the right renal pelvis and drained red, bloody urine. Her pain was relieved. A right retrograde pyelogram showed the previously noted radio-lucent areas even better outlined. They were most certainly blood clots. After a rather stormy course and persistent hematuria for three or four days, she improved and was discharged.

She was re-admitted in April, and again in May 1947, with almost exactly the same story as that outlined above. The concensus was that the source of the hematuria was definitely the right kidney, that the underlying cause was neither neoplastic, acid fast nor stone and, hence, that she should not be treated surgically. None of the observers had previously considered sickle cell anemia as a cause for recurrent hematuria of unexplained origin, and none could remember a similar case associated with sickling.

She is now pregnant for the second time and has been admitted to the obstetrical service in October and December 1947 with pyelitis of pregnancy. Her urine on both of these occasions showed red blood cells varying from "a few" to "too numerous to count" in addition to an Aerobacter aerogenes infection. She was last seen in the obstetrical dispensary on Feb. 5, 1948 with the complaint of recurrence of her severe, intractable nosebleeds and was referred to the nose and throat dispensary for palliative treatment.[3]

At the suggestion of Dr. Arnold Rich of the Department of Pathology, we undertook to review the histories of unexplained hematuria in Negroes in The Johns Hopkins Hospital from 1938 to 1947. The results were interesting and seem further to suggest some connection between hematuria and the sickle cell trait.

There were 86 cases of undiagnosed hematuria in Negroes in this period. A careful study of these histories however, showed that 67 of these had other associated disease or abnormality of their urogenital tracts such as severe infection, papillomata, urethral caruncle, renal cysts, hydronephrosis etc. which may have accounted for their hematuria. We thus excluded these cases as we were looking for those cases with otherwise "normal" urinary tracts, who had unexplained bleeding.

We finally ended our study of the histories with 19 cases of severe, gross, sometimes intermittent and recurrent hematuria in Negroes with apparently normal urogenital tracts. Many of these had been followed for a number of years. We believed that some of these 19 patients might fall into the same group as those already described. Of these cases, 6 had the sickling trait (cases 2 to 7 of this study). Two had no sickling. The other eleven had never been studied for sickling. A study of their histories, where such complaints as vague joint and abdominal pains and malaise are frequent, and where there are several cases of rather severe anemia makes us feel that more careful follow-up may uncover still others with sickle cell disease.

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[3] A recent review of the patient's chart indicates that she was admitted to the medical and obstetrical services at term, and in sickle cell crisis, in March 1948. She had intermittent, severe hematuria at this time. On March 31, 1948 she was delivered of a stillborn child. Recovery was satisfactory.

Three of these cases discovered in the review of the histories are abstracted briefly below. We have not followed them ourselves, and the notes on the histories are not clear as to whether the hematuria was as dramatically unilateral, severe, recurrent and unexplained as the preceding cases.

Case 5. T. H. (J. H. H. No. 143079), a 44 year old Negress, with a history of 3 episodes of gross hematuria between 1937 and 1941 was last seen in the gynecological cystoscopy clinic in September 1941. All three episodes were associated with right flank pain. The first two occurred during pregnancies, and the last was ten days post partum. Intravenous urograms were normal. A cystoscopy and retrograde pyelogram at the time of her last visit when she was not bleeding were not remarkable. She has been seen numerous times since then in the medical and orthopedic clinics with the complaints of vague chest and joint pains. There has been no recurrence of the hematuria according to the record. Her blood has never shown an anemia. The blood platelets were "normal" on several occasions. Her icteric index has varied between 6 and 8.

On one occasion in October 1939 one of the surgical house officers ordered a blood sickling preparation because of an indolent shin ulcer. This preparation was reported as showing 35 per cent sickling in 24 hours, establishing the presence of the "trait" without the anemia.

Case 6. J. S. (J. H. H. No. 124139), a 34 year old Negro, was admitted to the Brady Urological Institute where he was studied from June 15 to July 1, 1939 because of "essential" hematuria of approximately 6 weeks duration. One cystoscopic note indicates that the examiner thought he saw blood coming from both ureteral orifices. At a later examination blood was seen coming only from the left. His blood hemoglobin varied from 11 to 12 gm. per cent at that time. His platelet count was 234,000, and the icteric index was 3–5. Urograms were negative. As he was considered to be a case of unexplained hematuria, he was treated by Dr. Carl Burkland, who included him in his series of "essential" hematurias successfully treated with vitamin C. There is no record of any recurrence of his hematuria either then or on later visits.

He returned to the medical dispensary in June 1945 with the complaint of severe, persistent nosebleeds. Dr. Giles Filley, who saw him, made the presumptive diagnosis of sickle cell disease and ordered a thorough blood study. This revealed beginning sickling in 4 hours and complete sickling in 19 hours. His blood hemoglobin at this time was only 7.6 gm. per cent, and the icteric index was 6. On the basis of the characteristics of the sickling preparation he was considered to have the trait but not sickle cell anemia.

Case 7. A. B. (J. H. H. No. 150235) a 41 year old Negress, was last seen in this hospital in 1938 after she had been admitted to the gynecological service for 3 weeks for a hysterectomy and salpingectomy because of excessive vaginal bleeding. Her blood hemoglobin on admission was only 40 per cent of normal. There are no records of platelet counts, icteric index, or sickling preparations. On the fourth post operative day she had one severe episode of gross hematuria (catheterized urine), which slowly subsided in 3–4 days. She was followed briefly in two postoperative dispensary visits where the note states "no more hematuria." No attempt was made to investigate the cause of this episode of hematuria. It may have been related to the trauma of the operation; though this seems unlikely as it did not occur until the fourth post operative day.

The pathological sections in her case (Gyn. Path. No. 47316) showed: endometritis, chronic; myomata uteri; salpingitis, chronic; and follicular cyst of right ovary. When we became interested in her case, we reviewed the sections and were not surprised to find numerous sickle cells in the vessels of the uterus and ovary. Presumably she had the sickle cell trait. She had a profound anemia, and it is not known whether this was due to sickle anemia or to her prolonged vaginal bleeding.

DISCUSSION

Four cases of "idiopathic" unilateral renal hematuria occurring intermittently in Negroes with the blood sickling trait are presented. None of the commonly recognized causes of hematuria could be found in any of these cases, although the bleeding kidney was examined pathologically in two of the cases, and the other two were the subjects of careful clinical studies and observation as outpatients for 3 and 3½ years, respectively. Three further cases, with "essential" hematuria and the blood sickling trait co-existent, though unrecognized, are added from a study of the hospital records of unexplained hematuria in Negroes.

With the exception of the recent article of Abel and Brown (1948), we have been unable to find any reference in the literature concerning the coincidence of hematuria and sickle cell disease. This may be due to the rarity of such cases, or it may be that the possible significance of such a relationship has not been appreciated. This seems more likely to us in view of the fact that after seeing our cases one and three we were able to "rediscover" the other cases, which seem to fall so readily into the same category.

The second case presented a major clinical problem in the diagnosis of the cause of his hematuria, but the co-existence of the sickling trait was never suspected either during life or following autopsy until we were prompted by this study to review the autopsy slides.

The last three cases (Nos. 5, 6 and 7) gleaned from the hospital records of cases we have not seen personally, do not necessarily fall into the same group as the first 4 cases. In these, the hematuria, though unexplained, was not so severe or so prolonged and intermittent as those of the first 4 cases. Neither was it determined whether or not the bleeding was unilateral. However, the sickling trait was demonstrated in those cases, apparently as an incidental finding long after the hematuria was observed in cases 5 and 6, and as a result of our study of the pathological sections in case 7. The clinical records on the other 3 patients (Cases 1, 3 and 4) are filled with observations on blood sickling and the unexplained hematuria, and in case 4 the history of severe and frequent epistaxis is a very prominent part of the record. Yet the possible significance of the relationship between the blood sickling and the "renal epistaxis" in these patients was apparently not considered until we began this study.

The coincidence of "essential" hematuria and blood sickling in these Negroes raises the question of a causal relationship. There are not enough observations to make a statistical analysis, and it is impossible to say how often sickling might be associated with "essential" renal hematuria on a basis of chance. Wintrobe (1946) quotes the figure of 7.3 per cent incidence of the sickling trait in a series of 8453 Negroes (from the study of Diggs et al. 1933–1934). There are no figures available as to the incidence of unexplained hematuria in negroes but it is likely less than the incidence of the sickling trait.

Hinman (1935) says: "So-called 'essential hematuria' is not an entity and such idiopathic cases today most often are recognized as being caused by chronic unilateral or bilateral glomerulonephritis, arteriosclerotic nephritis, chronic passive congestion of the kidney, varices of the renal papillae (MacGowan), lead poisoning (Ockerblad), renal infarction and embolism, and causes outside the the urinary tract. Levy (1922), in a very thorough clinical study, found that the majority of these cases of bleeding for which no local cause could be found occurred in the fourth decade. This is the period when vascular changes might well account for many cases." It is noteworthy that our first 4 cases are in young patients and that the hematuria is gross, intermittent, severe, and unilateral and that in none of them were casts found in the urine. Busby and Anderson (1948) in reviewing 11 patients (with 12 pregnancies) at the Johns Hopkins Hospital, where pregnancy was associated with sickle cell anemia, found microscopic hematuria in two cases and gross hematuria in one case (D. S., our case 4). Dr. Frank G. MacMurray (1948) of the Department of Pathology has reviewed 82 cases of sickle cell anemia admitted to the medical and pediatric services. He has kindly given us his figures on the urinary findings, and they reveal that ten of these patients had microscopic hematuria ranging from a few to as many as 20 red cells per high power field at some time during their many admissions. Many of these findings may best be explained on the basis of the not infrequent glomerulonephritis and pyelitis associated with these cases. It is interesting however that the urinary findings were not constant during successive admissions or even in successive urine examinations during the same admission. One of the most striking of these cases when considered in relation to our 4 cases is that of E. A. (J.H.H. No. 155382) who had consistently negative urine examinations until the time of a severe "crisis" with cerebral manifestations and convulsions when showers of red blood cells, 5–10 per high power field, began to appear in his urine for a brief time. He is not included in our series because the bleeding was microscopic rather than gross, but there seems little doubt that the episode of bleeding in his case was related to the severe nature of the crisis of his disease, possibly by renal infarctions.

A consideration of the pathology of sicklemia is helpful in trying to explain the presence of hematuria in these cases. There is a marked tendency to infarction in this disease, and thrombus formation and infarction are most commonly seen in the spleen, lungs and kidneys. Diggs and Ching (1934) have suggested that these processes are probably due to "interlocking of elongated and spiked cells which are more hindered in transit through narrowed spaces than normal cells." Clinically there are many manifestations of infarction. Getzoff (1942) has discussed priapism in association with the disease. Connell (1942) has written of the neurological signs, and Zimmerman and Barnett (1944) and Yater and Mollari (1931), Bauer (1940), and Bauer and Fisher (1943) have described infarction of the kidney, acute glomerulitis, tubular necrosis, and bilateral massive necrosis as observed at autopsy. We have not been able to find any mention of red cells in the urine in reports of these cases, but believe that hematuria must have occurred, considering the lesions described, and such ante mortem diagnoses as acute nephritis and glomerulonephritis.

We believe that it can be concluded that sicklemia may cause hematuria through production of renal infarctions. Conversely, sicklemia should be considered as a possible cause of hematuria which is unexplained in terms of the more common causes of bleeding in Negroes.

Infarctions were not found to explain the renal bleeding, however, in our 2 cases from which the kidneys were available for pathological examination. Some other explanation must be found.

It is certain that there was no acceptable gross evidence of the cause for hematuria, although the barely perceptible hemorrhagic changes in the mucosa should be considered. The possibility of bleeding secondary to altered function and permeability of the capillary walls cannot be ruled out, although if this were the case other purpuric manifestations would be expected. There were none in our cases. According to Wintrobe (1946) epistaxis is frequently observed in sickle cell anemia, but purpura has not been reported.

There were microscopic changes in the small capillaries of the two kidneys which we were able to examine. These may have been due to irritation and inflammation secondary to repeated ureteral catheterization or they may have been the direct cause of hematuria. We believe that there is reason to consider the latter possibility.

Numerous cases of "essential hematuria" have been described in which similar capillary changes were evidently the cause of the bleeding. Cabot (1909) reviewed six such cases previously reported by Fenwick, and added another. Stephens (1922) described a case of "essential hematuria," very similar to our cases and occurring in a 28 year old Negro with a history of hematuria for 5 weeks. At right nephrectomy fine hemorrhagic spots involving many of the papillae were observed as well as a few dilated veins. On microscopic examination there were dilated veins and small hemorrhages into the substance of the papillae and free blood in some of the tubules. Priestley and Wilbur (1934) reviewed the clinical records of 100 cases of essential hematuria and the histology of the kidneys from 10 such cases. Of the microscopic studies they wrote: "In every instance changes were noted in the tips of the papillae, in the angle formed by the papilla and pelvis, or in the submucosa of the nearby pelvic tissue. . . .In practically every instance dilated blood vessels could be demonstrated in the tip of the papillae or beneath the surrounding epithelium. Most of the dilated vessels were thin walled venules or capillaries, either filled with blood or empty. Hemorrhage into the surrounding interstitial tissue was often associated. . . .The complexity of these veins, their relative dilatation and thin walls, and their close relation to the epithelium of the pelvis in these cases serve as an excellent basis for bleeding into the pelvis." They mention a similar group of 5 cases described by Wheeler in 1930. Webb-Johnson and Warwick (1941), studying lesions of the renal papillae, concluded that microscopic changes in the capillaries may often be the cause of severe "essential hematuria." Bobbit et al. (1944) included vascular changes in their classification of minimal changes responsible for so called "essential" hematuria. They described 2 cases with small capillary varices in the renal papillae which had evidently been responsible for massive hematuria. Thus many authors have agreed that pathology in the capillaries of the renal papillae may cause marked hematuria. They have been at a loss, however, to explain these vascular changes. Speculation concerning the etiology of the vascular lesions in the cases from the literature reviewed above is fruitless. We believe, however, that the minute thrombi arising from the conglutination of sickle cells could account for the capillary damage observed in the cases we have described. If this is the explanation, the pathogenesis could be as follows: minute intracapillary thromboses in some renal vessels due to the sickle cells (a process common elsewhere in the body in this disease), subsequent vascular stasis with damage to the capillary walls, and leakage of blood through these damaged walls into the collecting tubules, papillae and pelvis.

The fact, emphasized by Bauer (1940), that patients with unrecognized sicklemia are poor sugical risks makes the problem even more pointed. In case 1 nephrectomy was necessary because of the severity of the bleeding. Case 2 probably would not have died when he did if he had not been explored. Cases 3 and 4, we are following conservatively in the belief that any operative procedure would be a real disservice to them. It would, of course, be a great error to make the presumptive diagnosis of "hematuria associated with sicklemia" and to miss any of the commoner and more lethal causes of hematuria. We believe however, that cases of unilateral "renal epistaxis" in Negroes with otherwise "normal" urinary tracts should be studied for sickle cell disease.

If the diagnosis of sicklemia can be made in such a case, it should serve as an added factor to weigh in the often difficult decision concerning the advisability of operation. In doubtful cases, where neoplasm cannot be ruled out or where the hematuria is excessive, exploration and/or nephrectomy must still be the treatment of choice. The surgical parallel of this situation exists when the patient with known sickle cell anemia develops an acute abdomen which may be related to the sickle cell disease. In the face of the possibility of more severe disease, operation is almost always indicated. However, where these conditions do not exist, it may be to the best interests of the patient to temporize. In any event it is important to be forwarned concerning the existence of blood sickling and anemia in a contemplated operative risk. Careful blood studies in Negroes (as indeed in all patients) with unexplained hematuria should be mandatory.

SUMMARY

Four cases of "unexplained" gross, unilateral, renal hematuria in Negroes with the blood sickling trait are presented. Three additional cases, which were not so carefully studied, but which may be similar are briefly summarized and discussed. A table is included, summarizing the chief findings in these cases.

The pathology of sickle cell anemia is reviewed in an attempt to explain the hematuria on the basis of sicklemia.

Some of the literature on "essential" hematuria and on sickle cell anemia is discussed in a further attempted explanation.

The implications concerning these cases of hematuria and sicklemia are discussed.

CONCLUSIONS

Unexplained hematuria may co-exist with the blood sickling trait in Negroes. Kidneys of patients with "essential" hematuria usually show microscopic vascular changes in the papillae.

In the microscopic examination of the kidneys available in two of our cases there were vascular changes in the papillae.

These changes could be due to the effects of sicklemia, as described elsewhere in the body.

Some cases of unexplained gross hematuria in Negroes with the blood sickling trait may be related to the sickle cell trait.

Careful blood studies and sickle cell preparations should be made on the blood of Negroes with unexplained gross hematuria.

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An unusual retrograde pyelogram showed a constant defect at the outer portion of the middle calyx of the right kidney. One branch of the calyx showed an abnormality of position in that it lay in a plane at right angles to the other calyces. The dye was seen to surround peripherally a space occupying substance of homogeneous nature which extended outward from the region of the middle calyx, thus indicating a communication of the substance with the calyx. This was interpreted to be blood clot, tumor tissue, or inspissated pus in an abscess cavity. It was thought strongly probable that the wall of the calyx had been destroyed (fig. 1).

On November 11, 1948, under general anesthesia, the right kidney was explored through a flank incision. Projecting above the kidney surface, near its lower pole, was an irregular and lobulated tumor about two centimeters in diameter. Apparently the mass was contained within the renal capsule. Palpation of the renal pelvis revealed it to be partially filled with a soft mass. The kidney and proximal 3 inches of the ureter were removed and the patient had an uneventful convalescence (fig. 2).

The pathologist reported a nodule 3½ by 2½ cm. on the surface near the lower pole of the kidney which had invaded the capsule and had extended through the substance of the kidney into the pelvis. On section, in the center of the kidney a superior minor calyx was found filled with soft, white, partially necrotic tumor tissue which had protruded into the pelvis. Microscopic examination revealed a new growth poorly circumscribed by a thin fibrous stroma and lined by cuboidal and columnar cells resembling tubules. The nuclei of the cells were hyperchromatic but mitotic figures were rare. The cytoplasm of the cells stained poorly and appeared granular. The remainder of the kidney parenchyma was normal. The diagnosis was papillary adenocarcinoma, granular cell type (fig. 3).

SUMMARY

A case of papillary adenocarcinoma of the kidney has been reported because of the unusual x-ray findings after retrograde pyelography in view of a previous normal intravenous urogram.

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KIDNEY FUNCTION IN PATIENTS WITH PARAPLEGIA[1]

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The purpose of this investigation was to obtain information on some aspects of renal function of the paraplegic patient. Urinary tract infection and persistent alkalinity of the urine caused by urea splitting organisms are common. Persistence of this alkalinity, in spite of acid ash diet or occasionally even acidifying agents and inability to concentrate, as observed on a previous scout study, suggested a disturbed function of the tubular apparatus. Therefore, two tests were chosen. Phenolsulfonphthalein was used to test tubular excretion (Hanner and Whipple; Marshall and Vickers; Smith) whereas the dilution-concentration test served to evaluate tubular reabsorption (Chapman). Nonprotein nitrogen determinations were added routinely.

The investigated group consisted of patients with traumatic cord lesions, resulting either from bullet or shell fragment wounds or fractures of the spine, caused by accidents, and a few cases of non-traumatic myelopathy. All patients kept bedrest for the duration of the tests.

DILUTION: CONCENTRATION

The patients kept fasting 12 hours prior to test and wore an indwelling catheter in order to prevent errors due to residual urine. In the period preceding the test the patients were on a routine intake of 3,000–4,000 cc. of fluid per day in order to prevent dehydration. 1,000 cc of water were ingested over a 10 minute period at 8 a.m. while the bladder was completely emptied and this specimen discarded. Urine specimens were collected at 9 a.m., 10 a.m., 11 a.m. and 12 noon. At noon a dry lunch was offered, consisting of boiled meat, boiled potatoes and bread. Thereafter specimens were collected at 2 p.m., 4 p.m. and 6 p.m. Then a dry dinner, the same as lunch, was allowed and urine collected at 8 p.m. and 7 a.m. of the following day. Immediately following each collection the quantity and specific gravity of the urine were determined.

PHENOLSULFONPHTHALEIN

The patients fasted 12 hours prior to the test and wore an indwelling catheter. At 7:30 a.m. 600 cc of water were ingested at 7:45 a.m. the bladder was emptied, and at 8 a.m. 1 cc of phenolsulfonphthalein (calculated to deliver 0.6 mg. of the dye) was injected intravenously. 20 mg. of sodium bicarbonate were added into the drainage bottle. Four specimens were collected at ½ hour intervals and the first appearance of the dye was recorded. The specimens were immediately analyzed by the usual method for the percentage of the phenolred.

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[1] Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

RESULTS

The results were divided into four groups:

1) High concentration and low dilution (specific gravity above 1025 and below 1005 respectively)

2) Low concentration and low dilution (specific gravity below 1025 and below 1005 respectively)

3) Low concentration and high dilution (specific gravity below 1025 and above 1005 respectively)

4) High concentration and high dilution (specific gravity above 1025 and above 1005 respectively)

The phenolsulfonphthalein excretion in these four groups is shown in table 1.

Among the 70 patients tested, 33 (47.14 per cent) were in group 1 with a normal range of concentration and dilution. The average excretion of phenolred for this group was 60 per cent. Of the 33 patients in group 1, 13 (39.39 per cent) had a dye excretion within normal limits.

TABLE 1

CLASSIFICATION . . Concentration Dilution.	GROUP 1 Concent High Dilution Low		GROUP 2 Concent Low Dilution Low		GROUP 3 Concent Low Dilution High		GROUP 4 Concent High Dilution High	
No of Patients .	33		33		4		0	
Average of PSP Excretion in %	60%		49%		57%		0	
Dye Excreted	No of Patients	Per cent	No of Patients	Per cent	No of Patients	Per cent	No of Patients	Per cent
%								
80	4	12.12	0	0	0	0	0	0
70-80	9	27.27	2	6.06	0	0	0	0
60-70	6	18.18	5	15.15	2	50%	0	0
50-60	9	27.27	15	45.45	2	50%	0	0
40-50	4	12.12	3	9.09	0	0	0	0
30-40	1	3.03	5	15.15	0	0	0	0
20-30	0	0	3	9 09	0	0	0	0

Thirty-three (47.14 per cent) of the 70 patients belonged to group 2 with a low concentration and low dilution. Their average phenolsulfonphthalein excretion was 49 per cent and only two (6.06 per cent) reached a normal phenolsulfonphthalein value.

Only four patients (5.72 per cent) of the 70 tested appeared in group 3 with low concentration and high dilution. The phenolsulfonphthalein excretion averaged 57 per cent and none of these four patients reached a normal value of dye elimination.

The nonprotein nitrogen determinations were within normal limits in all of the 70 patients.

DISCUSSION

Volhard's concentration-dilution test lends itself to examine one function of the tubules, namely reabsorption, as it is known that approximately 99 per cent

(Best and Taylor) of the excreted fluid is reabsorbed by the tubules. Under normal conditions the specific gravity of urine is inversely proportional to the volume. The fluid eliminated during the test should almost equal the ingested amount within the first 4 hours, with dilution to 1005. Thereafter gradual concentration should occur to a minimum of 1025 with a decreasing output.

In analyzing the results of the urinary output during the 4 hour period the following points were noted: The average maximum output was reached within 2 to 3 hours. Five cases showed an excretion of more than 1500 cc. Two of these cases fell into group 2 with presumably decreased tubular function. Eleven cases revealed an excretion of less than 500 cc with 6 cases falling into group 2 and the remaining 5 cases into group 1. This observation is hard to explain inasmuch as all patients were on adequate fluid intake prior to the test. All 6 cases with reduced excretion in group 2 had persistent albuminuria, which might indicate glomerular damage. Interpretation of this failure of urine dilution is at present impossible. Loss of glomerular surface or circulatory insufficiency are possible mechanisms.

Four cases in group 3 revealed an unphysiologic diluting and concentrating power, with likely damage to glomeruli and tubules.

In evaluating the concentration portion of the test it was found that out of a total of 70 patients 37 (52.85 per cent) achieved a concentration of less than 1025. Of these 37 patients, 33 had a normal dilution. These cases are considered in the discussion of correlation between the amount of dysfunction and the level and completeness of the spinal cord lesion and the nonprotein nitrogen determination.

Since the original work by Rowntree and Geraghty numerous authors have investigated the mechanism of the phenolsulfonphthalein (PSP) test, and its theory and practical application has been authoritatively presented by Homer Smith. It is now accepted that a major portion (80 per cent) of the intravenously administered phenolred undergoes a chemical union with the protein fraction of the blood, is taken up by the cells of the body and is then gradually released for excretion. 94 per cent of the total dye is eliminated by tubular excretion. The only place where dye was not detected is the brain and spinal fluid. Inasmuch as a considerable portion of the dye is protein bound, this portion does not pass the glomerulus under physiologic conditions. Another proof that the dye is not eliminated by the glomerulus is the presence of dye in the urine of cases with low blood pressure, insufficient for glomerular filtration.

Under physiologic clinical conditions 70–80 per cent of the dye are retrieved from the urine and the remainder is excreted by the liver and bile ducts. In pathological states of liver or kidney the other organ increases phenosulphonphthalein excretion to partially compensate (Major). Anemia has no effect on the phenolsulfonphthalein excretion (Chapman) but acidosis tends to decrease it and alkalosis increases it (Marshall and Vickers).

The general result of our investigation revealed that the average excretion was 20–30 per cent below this normal 70–80 per cent. In group 1 in which the dilution concentration test was physiologic only 13 cases (39.39 per cent) showed a normal dye excretion. This would indicate that the phenolsulfonphthalein test is more sensitive than the dilution-concentration test, contrary to Volhard's conception. It seems to indicate furthermore that tubular excretion is earlier disturbed than tubular reabsorption.

In group 2 there were only 2 cases (6.06 per cent) within normal limits for dye excretion. The impairment of tubular function in group 2 is also illustrated by the drop of the average excretion of phenolred to 49 per cent from the average of 60 per cent in group 1.

No normal value of excretion of dye was found in group 3, although the average excretion went up to 57 per cent. It is conceivable that due to albuminuria some of the protein bound dye passes the glomerulus and appears in the urine, although one would expect this amount to be rather small.

The appearance time averaged 5–8 minutes. The averages ranged from 5 minutes in dorsal lesions to 5.5 minutes in lumbar lesions and 7 minutes in cervical lesions.

In correlating the results of the nonprotein nitrogen determinations with those of the other tests it was found that a normal nonprotein nitrogen value was present in cases with impaired tubular function, demonstrated with one or both above mentioned tests. When the time interval after injury and the level of injury were plotted against kidney function, no correlation was found among the dorsal and lumbar lesions of group 2, twenty of which were injured more than 20 months and 13 patients less than 20 months. Only cervical injuries seemed to reveal tubular damage at an earlier time than other levels. Among 8 cases with a vertebral level of C-6, seven fell into group 2 and the majority showed damage within 15 months. It remains undetermined whether or not the impaired vascular control of the splanchnic bed is responsible for this fact. On plotting the extent of the injury against the amount of kidney dysfunction no correlation could be demonstrated. In group 2 there were 20 cases of complete and 13 cases of partial cord severance.

In 7 cases there was a history of kidney calculi. The kidney function in 2 cases following removal of kidney calculi was better than in the remaning 5 cases in which no attempt of removal was made Three cases had undergone nephrectomy at an earlier date; their kidney function was comparable to that of patient with bilateral kidneys.

SUMMARY

Seventy cases of spinal cord lesions, chiefly of traumatic origin at various levels were subjected to a dilution-concentration test, phenolsulfonphthalein test and nonprotein nitrogen test.

Thirty-seven patients (52.85 per cent) revealed abnormal findings on testing dilution-concentration. Thirty-three patients (47.14 per cent) showed an inpaired ability to concentrate and four patients (5.72 per cent) revealed a combined impairment of dilution and concentration.

Fifty-four patients (77.14 per cent) revealed an impairment of phenolred excretion and only 16 patients (22.85 per cent) attained a normal value of dye excretion.

The nonprotein nitrogen determination was normal in all cases and is a late criterion as compared with the other two tests.

The phenolsulfonphthalein test revealed impaired tubular excretion with normal tubular reabsorption in 17 cases (24.28 per cent) and suggests that tubular excretion may be earlier damaged than tubular reabsorption in these cases.

Only cervical lesions seem to reveal a correlation between the time interval after injury and kidney function, among 14 patients 8 cases (57.14 per cent) showed tubular impairment within 15 months. This correlation does not apply to thoracic or lumbar lesions.

There is no correlation between the extent of cord damage and the amount of kidney dysfunction.

Dysfunction is apparent in cases of renal calculosis.

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INTERSTITIAL CYSTITIS[1]

JAMES A. SEAMAN

The basic syndrome of interstitial cystitis is excruciating pain in the bladder region, relentless frequency day and night, and often urgency to the point of incontinence with urine that is usually macroscopically clear and in small amounts. Occasionally it shows some blood and more often shows microscopically only a few red blood cells and pus cells. Add to this persistency and chronicity. There are, to be sure, variations of this syndromic curiosity. It is notoriously an affliction of the middle-aged female and rarely the male. It is essentially a distaff disease. I have never seen it in the male and only once in a 24 year old woman. Cases have been reported by Hand, Kretschmer, Higgins and others who have seen it in the ages from 17 to 24. My oldest patient was 84 and had had a checkered urinary career for 15 years.

Although the condition had been previously observed and reported by others, both here and abroad, it remained for Hunner, in 1914, to present the classical clinical and pathological condition and to alert the American urologists to the entity. The term "interstitial cystitis" seems to epitomize the pathological picture better than the fourteen other names by which it has been designated and which seem only to confuse the issue. It is elusive today only as to its etiology and if present at all, should be detected anatomically, if care and the proper technique are used.

Many hundreds of cases have been reported by careful observers and considerable experimental work has been done but just when it seems as if the problem has been solved, the elusive cause escapes. The further we get away from etiology, the more we stress treatment, most of which is palliative and none curative.

Hunner believed that the cause of the condition was an infection in the kidney with a resultant stricture of the ureter and the organism was the Streptococcus viridans originating in the teeth or tonsils. Papin states that it is not of tuberculous, specific or neoplastic origin, nor traumatic or neurogenic causes. Meisser and Bumpus, following the experimental work of Rosenow, felt that a streptococcus with a selectivity for the urinary tract was the cause. Attempts have been made to reproduce the lesion by tying off the vessels to the bladder (Herbst). Winsbury-White demonstrated lymphatics going to the bladder from the cervix. From the standpoint of infection, it would seem logical to suspect some source of infection near home such as this. There may be more merit to this than appears at the first blush. Along the same line of reasoning, Powell felt that the obstruction in the lymphatics of the bladder could be responsible for a lymphatic edema in the vesical wall. Davis tried various dyes without satisfactory results. The area of the cystitis has been biopsied, resected, macerated and cultured without recovering an organism which tempts one to believe that the organism has long since been destroyed, and the reaction to the inflammation established long before the patient is seen. It is infinitely possible that there have been repeated episodes of cystitis over periods of time with or without the patient's knowledge. It is well known that the vesical mucosa is relatively insensitive and that many women have varying degrees of cystitis without being aware of it.

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[1] Read at annual meeting, American Urological Association, Los Angeles, Calif., May 19, 1949.

One condition which is very common, yet not mentioned in any of the reports examined, is endocervicitis. It has been present in varying degrees in every case of interstitial cystitis observed by the author. The incidence of urinary tract infection from this source is perhaps the most common among all causes of urinary tract infection in the female and is responsible for the occurence of the 40 per cent more infections in the female genito-urinary tract than in males.

It is readily explicable therefore why there are some reports of positive cultures from the urine found by some authors. It may well be that they are dealing with another acute or subacute cystitis in the long course of repeated infections from below. The granular urethritis so often found could be explained on this basis as well. Always the organisms reported are the usual ones found in the cervix. Whether these organisms reach the vesical wall through the lymphatics which Winsbury-White and Powell point out exist between the cervix and the bladder, or whether they reach the bladder directly through the urethra, or by contiguity, is a moot question. Suffice it to say that the organisms do get there and, after repeated attacks of cystitis, the background is laid down in the vesical wall. Then comes the attack which precipitates the severe symptoms, which attack in itself and by itself would not have done so. It finds the capillaries dilated and the arteriols thickened, the venous structures dilated and the lymph channels compressed. The reaction to the inflammation is now severe. The tissues are unable to ward it off and we get the edema and extensive leukocytic infiltration about and within the nerve sheath causing severe pain. Hand believes this last is the essential pathology of the disease. It may well explain the improvement in pain after dilation of the bladder and fulguration of the lesion by improving circulation and carrying off the edema around the nerve sheath.

OCCURRENCE

The lesion may be single or multiple and usually occurs on the dome or walls of the bladder. Sometimes they are seen on the bas fonde. Some observers have seen the lesion on the trigone. The writer confesses that he has never seen it here. Why it never seems to involve the ureters is inexplicable. It occurs in women of any age but more frequently in those between 40 and 60 years. Social and marital status have no significance. It has no relationship to venereal disease, tuberculosis or other systemic diseases. It is doubtful if cancer ever develops from it except by coincidence. The author has seen 3 cases of vesical cancer with accompanying interstitial cystitis and he is reasonably sure that one had nothing to do with the other. They both occur in the cancer age.

PATHOLOGY

The typical lesion has the appearance of a submucous fibrosis closely underlying the mucous membrane and arranged in an irregular stellate pattern. Perhaps this could be more accurately described as an octopus fashion with the tentacles, thick or thin, extending irregularly outward from the center, which may be no bigger than a few millimeters. The tentacles are of varying lengths, ranging from one half a centimeter to two or more centimeters. Sometimes it appears as if the bands of scar tissue were actually lifting up the mucous membrane. The mucous membrane overlying these strands or tentacles is smooth and often glistening in the resting state of the bladder. Where these bands converge one may sometimes observe some slight excoriation of the mucous membrane. There may be a palish hue to the area, and sometimes a light red blotchiness here and there. The whole mucous membrane may be so red from a recent cystitis as to mask the entire picture and make it impossible to recognize the lesion. Sometimes the bands from one area will pass by or join with others from another area.

One gets the impression of a certain fixity to the region involved. This becomes an actuality when one studies the dynamics of the bladder under anesthesia and watches the areas as the organ slowly fills. When the tolerance of the bladder is reached, which is rarely more than five ounces and more often three or four ounces, there appear along the bands, as they are stretched, little beads of blood. The area will then definitely appear fixed while other portions of the bladder wall continue to dilate a little further. The water will stop flowing in because the capacity of the bladder has been reached. The lesion may be localized in one small area or may extend through the entire wall of the bladder. In long standing cases the bladder wall throughout is involved and the organ is like a leather bag, without any distensibility whatever.

Microscopic sections through the wall of the bladder show the picture of inflammation plus the deposition of fibrous tissue in the submucous region. Under this is seen round cell infiltration in varying degrees extending through the muscular wall. The capillaries are dilated, as are the venules with plugging of the lymph vessels. There is leukocytic infiltration of the nerve sheaths. Tissue staining has failed to demonstrate the organism.

SYMPTOMS

Usually the onset is insidious but there are instances in which it begins where an acute cystitis leaves off. This time the apparent simple infection doesn't seem to clear up as expected. It is much like the third or fourth attack of appendicitis which fulminates and demands surgery; the others just left the scars. The pain becomes excruciating and persistent day and night, allowing very little sleep until the patient really does become a nervous wreck. Most women can endure all kinds of pain but this pain overwhelms them. They become socially recluse, staying as near the bathrooms as possible. The pain is knife-like and persistent and becomes more intense when the bladder fills to its maximum capacity of three to five ounces at best. When the urine is held longer, gross blood usually appears in the urine from the stretching of the scar tissue under the mucosa causing minute cracks in the latter, and bleeding. The patient rarely waits that long or can wait that long before emptying the bladder. If there is no immediate facility for voiding, the patient loses her urine.

The symptoms are so disproportionate to the actual lesion and the urinary microscopy so palpably negative as to suggest some other pelvic cause of the agonizing pain. It is not to be wondered at therefore, that the ovaries, verted uteri and misplaced appendix or something in the rectum is thought to be the cause of the pain unless one closely follows the history which alone almost tells the story and observes the precise nature of the pain. The patient will often put her finger on the exact spot overlying the lesion. The pain may radiate to the vagina or rectum or hip. Endometriosis might well be suspected and, vice versa, the pain of the endometrial walled-cyst attributed to interstitial cystitis. Menstruation causes the pain in each instance to increase.

Most of these patients dread cancer and fear that it is the problem. They delay for a while henceforth, but when they finally do seek medical advice, the physician is likely to be beguiled by the essentially negative urine. The sterile urine with a rare blood cell is easily disregarded, especially in the female. Cystoscopy, the most important diagnostic means we have, is not even suggested. The patient is treated for a list of conditions with emphasis on her "neurosis." The discouraged patient goes along for many months (more often many years, 5, 10 and longer) before a diagnosis is made. The only other disease with such low diagnostic index is probably endometriosis which has a comparable frequency of incidence. And yet the diagnosis of this particular type of cystitis can usually be made at the bedside if one remembers the character of the pain, its persistency and chronicity, the small capacity of the bladder with its frequency and clear urine, occurring in a patient from forty years on usually and for whom no treatment has been availing.

DIAGNOSIS

The carefully taken history usually tells the story. The chronicity and severity of the pain with frequency of small amounts of clear urine and the patient having been treated for some time, often by many operations, without relief, give a strong hint of the nature of the trouble. One must not be misled by finding considerable pus in the urine due to recent acute cystitis or pyelitis. It is therefore, not necessary for the urine to be sterile or free of red or white blood cells. The acute cystitis may obscure the lesion. If it does, the patient should be subjected to cystoscopy when the bladder infection has subsided. The cystoscopy should be conclusive. The writer has never seen the acute lesion. It is always the exacerbated form of the chronic condition. One should not mistake the coarse trabeculation of the prostatic's bladder (or other obstructive uropathy) or the fine trabeculation of the neurogenic bladder or in the bladder of a cystocele when there is a patchy catarrhal cystitis overlying it. There are times when the similarity is very deceptive. These conditions do not meet the criteria of interstitial cystitis.

TREATMENT

In a disease with such an obscure etiology, though a definite symptomology and pathology, it is but expectant that the treatment might be empirical and varied. Since Hunner first clearly defined this entity, various forms of therapy have been used with varying degrees of success and failure. Foci of infection in the teeth, tonsils and elsewhere have been eradicated, infections in the upper urinary tract have been cleared up, the lesions have been fulgurated, excised, treated by x-ray, and lavaged with silver nitrate and with various dyes. Urinary antiseptics and biologicals have been used, including hormones, with indifferent success. Perhaps not enough attention has been given to the nearest and perhaps the most obvious source of infection in the endocervix. Presacral neurectomy has proved ineffective.

After assuring oneself of the correct diagnosis, the first logical step is to relieve the fixation of that involved segment of the bladder. This must be done under an anesthetic. The writer prefers sacral anesthesia using 1 ounce of ordinary 1 per cent novocain. It matters little what preference one has. Then with extreme gentleness, the cystoscope is introduced and the dynamics of the bladder observed while the water is allowed to enter very slowly. As the pressure approaches the capacity for the particular bladder, the area of the lesion will at once stand out and be restricted in its further dilation while the unaffected portions of the bladder will continue to expand. There is no pain so the bladder may tolerate a little more than the patient could without an anesthetic. The involved area will become static and small cracks will appear in the mucous membrane along the strands of fibrosis and tiny beads of blood will be seen which are washed away by the fluid being used. The inflow of water will usually stop and even increased pressure will not budge the affected area but only cause it to bleed more. A small insulated wire electrode is then introduced and, with a fine cutting current, the bands are sliced transversely wherever they seem to hold. The area at the incision is seen to pull apart as the current of water continues to flow and the increased capacity of the bladder becomes apparent immediately, thereby proving the inhibiting effect of the fibrous tissue.

Sometimes more bands are seen in the clefts caused by cutting and these too are incised. No attempt should be made to go deeper because the bladder wall at this point may or may not be thickened. The incising should not be ruthless but delicate as it were, cutting gently and superficially always until one is quite sure that there are no more restraining bands. There will be some bleeding which is readily controlled by a light coagulating current. With a blended current there is little or no bleeding. The job is painstaking and should not be rushed.

The writer sees no advantage in "spraying" the area with a fulgurating current. The real lesion is under the mucous membrane and simply going over the surface does not reach the submucosa. Sometimes a Foley catheter is placed in for a very few days and sometimes longer, if the patient has to be kept in bed for any other condition,—and the bladder is then treated as in a case of simple cystitis, with one difference: It is essential to keep the bladder capacity as high as possible or slightly under what was attained at the operation. Silver nitrate lavages, preceded by 1 ounce of 4 per cent novocain, which is left in for a few minutes, are used daily. The catheter is then irrigated gently with warm 1–1,000 silver nitrate solution after first lavaging with warm sterile water, the fluids gently distending the bladder to the point of tolerance each time. The patient could go home at the sigmoid. When the bladder was opened, only normal mucosa was seen, but histological examination of the site of the tumor showed solid plugs of carcinoma cells in the muscle layer of the bladder. The second case of an infiltrating tumor of the bladder showed complete absence of carcinoma in the excised specimen, although several sections were examined.

Hellstrom[16] of Sweden observed that "many papillomatous bladder tumors may markedly subside after ureteral implantation."

These cases show that clinical regression and dissolution of bladder carcinoma following sidetracking of the urine do occur and that further attention should be directed to the possible biologic significance of this phenomenon.

CASE REPORT

E. F., male, aged 55, was seen February 17, 1947, complaining of frequency, nocturia 2–3 times, and urgency of 8 months' duration. These symptoms lasted for periods of a few days, recurring every 3 weeks. There was no burning on urination, dysuria or gross hematuria. The recurrent attacks became more frequent, the intervals free of symptoms being less than one week. The past history was irrelevant.

Physical examination was negative except for a slight degree of deep tenderness over the left costovertebral angle. The prostate was not enlarged and the secretion contained only a few white blood cells per high power field. There was no residual urine. Urinalysis showed only 5 white blood cells and 5 red blood cells per high power field in the centrifuged specimen. The blood count was not significant. A plain urogram was normal. Cystoscopy revealed several small subsessile papillary growths on the right lateral wall and floor of the bladder with several adjacent dull-red velevety-appearing circumscribed areas suggesting an infiltrating type of lesion. The bladder soon became irritable and spastic. Several specimens were removed for biopsy and subsequently reported as "apparently edematous portion of papillomatous structure from the bladder, inflammatory in origin."

Cystoscopy was repeated 2 months later (April 1947). The bladder mucosa appeared to be congested, dull and velvety on the floor and trigone, with several scattered small similar patches on the anterior wall. One small clump of benign-looking papillary growth was noted in the right fornix region consisting of three discrete villous papillomata, 1 cm. in diameter in toto. A diagnosis of a patchy chronic cystitis with small papillomata was made and 1 week later these were destroyed by cystoscopic fulguration. Urinalysis continued to show many red blood cells and a slight gross hematuria on several occasions was reported by the patient.

Cystoscopic examination on August 5, 1947 again demonstrated patchy, dull, velvety areas on the mucosa with 2 small sessile, irregular papillary growths in the right fornix (as noted four months previously) together with another sessile papillary area on the anterior wall near the air bubble. The bladder went into spasm within a few minutes following the introduction of the instrument. A

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[16] Hellstrom, J.: Some views on the treatment of vesical tumors, especially ureteral. Urol. & Cutan. Rev., 52: 385, 1948.

Many sections from various parts of the bladder were taken for microscopic study, and were carefully examined by the pathologist (Dr. Weintraub). Only chronic cystitis involving the mucous membrane was disclosed. No tumor cells could be found in any of the numerous sections.

Convalescence was satisfactory except for a hyperacute left epididymo-orchitis 3 months following the cystectomy and 1 week after having returned to work. This necessitated an orchiectomy.

Intravenous urography in August, 6 months postoperatively, revealed good secretion, concentration and drainage of the dye with absence of any back pressure changes as evidenced by bilateral normal appearing pelves (fig. 2).

When last seen in November 1948, the patient was working regularly and passed urine per rectum about every 4 hours during the day and only once at night.

COMMENT

This additional case of spontaneous regression of a bladder tumor following diversion of the urinary stream is reported to direct attention to the curability of carcinoma, especially in the urinary excretory tract.

Complete excision of malignancy, when amenable, is still considered the surest way to handle this condition, although the etiology of such growth remains beyond the boundaries of scientific knowledge. Apparently, the tumor, in this particular bladder, regressed completely, either because the removal of urinary carcinogens removed the chemico-biologic irritation which produced cancer in a susceptible sensitized urothelium, or by being placed at rest, the natural capacity of the mucosa to heal effected dissolution of bladder carcinoma following side-tracking of the urine, even in the short period of 3 weeks.

The mechanism of urinary tract carcinogenesis, as expressed by Gaultieri et al.[11], namely, "An histologically abnormal urothelium; sensitized by a prerequisite combination of general and local factors or influences; urothelial activation by a catalyst carcinogen; perpetuation of growth by specific tissue enzyme action," should be considered as pointing the way to a satisfactory working hypothesis, especially since they are convinced that the process is a reversible one. This process is apparently demonstrated by this case, as well as those cited by Pearse, Trabucco, and Davis.

SUMMARY

A case of infiltrating papillary carcinoma of the bladder is presented which showed a spontaneous regression of the tumor in the bladder removed by a complete cystectomy three weeks following a bilatral ureterosigmoidostomy.

Although such an extraordinarily satisfactory result is extremely rare, similar good results have been reported recently in a few other instances following ureterosigmoidostomy. The procedure is not advocated as a curative measure, but it does direct attention to the question of a carcinogen, exogenous or endogenous, as an ingredient of urine.

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LYMPHOSARCOMA OF THE URINARY BLADDER: CASE REPORT

HARRY M. BURROS, JOHN F. DRAPIEWSKI AND JAMES B. PURCELL

The purpose of this paper is to report a case of primary lymphosarcoma of the bladder, the rarest of the varieties of vesical tumors.

This case is the ninth to be reported. G. E. Moloney described the last case in July 1947 while the literature was thoroughly reviewed in January 1947 when Levant and Rosenfeld reported the seventh case on record.

A woman, aged 68, was admitted to the hospital with the chief complaint of bloody urine. She was apparently well until 5 months prior to admission when blood was first noticed in the urine. This continued intermittently until admission and in the 3 months before hospitalization the hematuria was accompanied by symptoms of dysuria and frequency, both diurnal and nocturnal. During the last 3 weeks she complained of pain during and just after voiding. The past history did not suggest any previous urinary difficulty. Physical examination disclosed only slight tenderness in the suprapubic area. No mass was palpable either externally or by bimanual examination. No lymph nodes were palpable.

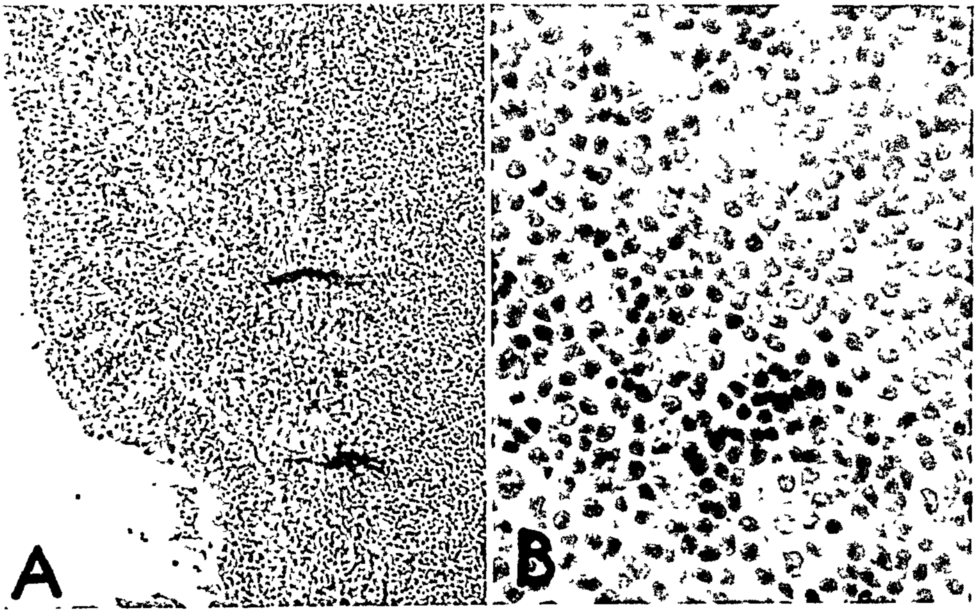

FIG. 1. *A*, lymphosarcoma of bladder, showing mucosal surface. *B*, lymphosarcoma of bladder, showing high power of tumor cells.

The urine was red, loaded with erythrocytes and many Gram negative and Gram positive organisms were present. Other laboratory studies were all within normal limits. Intravenous urography showed a filling defect in the dome of the bladder and cystoscopic examination disclosed a tumor in the midline of the superior aspect of the bladder. The growth was well demarcated from the surrounding bladder mucosa which had a normal appearance.

Nine days following admission segmental resection of the bladder was performed under spinal anesthesia. The growth was removed with a large cuff of apparently normal bladder and a small portion of the peritoneum which was involved. The postoperative course was uneventful and the patient was discharged, wound healed and voiding without pain or bleeding, 2 weeks following the surgery.

The gross specimen consisted of a firm, fibrous, hemispherical mass of tissue measuring 6.5 by 6.5 by 4.0 cm. The rounded aspect of the specimen was mottled red-brown and showed several small ulcerated areas. The cut surface was beefy red and had a glistening, somewhat mucoid appearance. Also included was a fragment of tissue resembling thickened peritoneum measuring 4 by 4 by 0.5 cm. One aspect showed a patch of conglomerate petechial hemorrhages. The other aspect displayed a group of red-brown nodules the largest of which was 0.3 cm. in diameter.

Microscopically the epithelium overlying the tumor was of the transitional variety and was mature and well differentiated. It showed areas of squamous metaplasia. The tumor itself consisted of a solid mass of small cells indistinguishable from lymphocytes. A few mitotic figures were present. There was very little stroma in the lesion. The tumor deeply invaded the wall of the bladder and in some sections it appeared on the peritoneal surface. The line of resection passed through the margins of the neoplasm. Stains for mucus were negative.

At the time this report was made the patient was living and symptom-free two and one half years following operation. Cystoscopic examination showed an indurated area in the dome of the bladder but no evidence of a recurrence of the growth.

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A STUDY OF UNTREATED BLADDER CANCERS

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While the literature dealing with the treatment of bladder tumors is voluminous, only scattered references are available with regard to the length of life of patients with untreated bladder cancer. Farber determined that the mean duration of the disease was 18.8 months in a series of 33 patients with approximately 10 per cent of them surviving more than 5 years. Similar figures were presented by Welsh and Nathanson who found that 90 per cent of 28 patients with untreated bladder tumors were dead 5 years after the onset of symptoms. A proper evaluation of the data in these reports is difficult because neither macroscopic nor microscopic description of the lesions was given.

It is the purpose of this report to add a series of 60 untreated bladder cancers to the literature. Fifty-eight of these cases received no treatment and 2 of the cases received treatment considered insufficient to alter the natural course of the disease. Fifty-six of the 60 patients were considered unsuitable for treatment when first seen at the Roswell Park Memorial Institute because of far advanced lesions. Four of these patients had distant metastases, 35 had extension of tumor growth beyond the bladder and 17 had uremia due to ureteral obstruction from extensive carcinoma. Of the remaining 4 patients, 1 died before treatment could be instituted, 1 refused treatment and 2 had received totally inadequate therapy, the effect of which was not thought to alter the course of the disease (table 1).

In 54 of these 60 untreated bladder cancers biopsy or autopsy specimens were available for study and a review of the material revealed the following histological findings: 35 patients had nonpapillary infiltrating cancers, 16 had papillary infiltrating cancers, 1 had adenocarcinoma and 2 patients with clinically extensive papillary infiltrating tumors had microscopically no demonstrable evidence of infiltration. In the remaining 6 cases no positive biopsy could be obtained because the presenting parts of the tumor were necrotic. However, the clinical and cystoscopic findings were characteristic of infiltrative vesical cancer which had spread beyond the limits of the bladder (table 2). The figures presented in table 3 apparently justify the decision to withhold treatment of this group of cases since the average duration of life from the time of admission to death amounted to only 3.9 months. Fifty per cent of the patients died of the disease in less than three months, 76.6 per cent were dead within 6 months and 93.3 per cent were dead in less than 12 months. Of the 4 patients who survived more than 1 year, 3 died between 1 and 1½ years, and 1 died after 1 year and 9 months.

The actual duration of life from the onset of symptoms to the time of death has been summarized in table 4 from which it is evident that the 60 patients survived for an average of 13.2 months. The mean duration of the disease was 10.4 months in the group of nonpapillary solid infiltrating cancers as compared to

TABLE 1. *Reason for not being treated*

	EXTENSION BEYOND BLADDER	EXTENSION BEYOND BLADDER AND KIDNEY INSUFFICIENCY	DIED BEFORE TREATMENT COULD BE INSTITUTED	REFUSED TREATMENT	METASTATIC	INSUFFICIENT AND INCOMPLETE TREATMENT	TOTAL
Solid infiltrating	24	7	1	1	3		
Papillary infiltrating	6	9			1	2	
No biopsy	5	1					
Total	35	17	1	1	4	2	60

TABLE 2. *Histology of 60 tumors*

No biopsy—clinically infiltrating		6
Solid infiltrating carcinoma		
Group I	6	
Group II	10	
Group III	9	
?	7	
Epidermoid	3	
		35
Papillary infiltrating carcinoma		
Group I	1	
Group II	9	
Group III	2	
?	4	
		16
Papillary carcinoma		4
Adenocarcinoma		1
Total		60

TABLE 3. *Length of life after admission*

	SOLID INF. CA.	PAP. INF. CA.	PAP. CA.	ADENO-CA.	NO BIOPSY	TOTAL
Less than 3 mos.	16	9		1	4	30
3–6 mos.	11	4	1(3 mos.)			16
6–9 mos.	5	1			2	8
9–12 mos.	2					2
1–1½ yrs.	1	1	1(13 mos.)			3
1½–2 yrs.		1				1
Total	35	16	2	1	6	60
Average	3.6 mos.	4.7 mos.	8 mos.	2 mos.	3.0 mos.	3.9 mos.

TABLE 4. *Length of life after first symptoms*

	SOLID INF. CA.	PAP. INF. CA.	PAP. CA	ADENO CA.	NO BIOPSY	TOTAL
Less than 3 months	2					2
3–6 mos	8	2		1		11
6–9 mos	3	2	1(6 mos.)		1	7
9–12 mos	8	2				12
1–1½ yrs	7	4			2	13
1½–2 yrs	4	1	1(19 mos.)		1	7
2–3 yrs		2			1	3
3–4 yrs	1	1				2
4–5 yrs						
over 5 yrs					1	1
unknown	2					2
Total	35	16	2	1	6	60
Average	10.4 mos.	14.5 mos.	12.5 mos.	5 mos.	24.3 mos.	13.2 mos.

TABLE 5. *Length of life after admission in treated cases*

	SOLID INF. CA.	PAP. INF. CA.	TOTAL
Less than 3 mos	8	5	13
3–6 mos	5	3	8
6–9 mos	10	6	16
9–12 mos	6	4	10
1–1½ yrs	5	7	12
1½–2 yrs		1	1
Total	34	26	60
Average in months	7.1	9.3	8.0

TABLE 6. *Length of life after onset of symptoms in treated cases*

	SOLID INF. CA.	PAPILLARY INF. CA.	TOTAL
Less than 3 mos			
3–6 mos	3		3
6–9 mos	4	2	6
9–12 mos	6	3	9
1–1½ yrs	15	10	25
1½–2 yrs	3	6	9
2–3 yrs	3	4	7
3–4 yrs			
4–5 yrs		1	1
over 5 yrs			
Total	34	26	60
Average in months	13.5	18.5	15.7

phosphatase 4.5 units per 100 cc. Both blood samples were examined immediately after withdrawal and neither showed any evidence of hemolysis.

On x-ray examination of the chest, spine and pelvis, no abnormalities were seen and there was no evidence of metastases. On August 14, 1948 a suprapubic prostatectomy was performed. At operation the adenomas were easily enucleated and the gland was considered to be clinically benign.

Pathological examination (Dr. D. W. Penner): "The specimen consists of two segments of prostate measuring 3 by 3.5 by 2 cm. and 6 by 4 by 3 cm., together weighing 76 gm. Serial sections reveal two red hemorrhagic areas 2 cm. and 1.5 cm. in diameter in the larger segment. Microscopic examination shows recent red infarcts of the prostate. No evidence of carcinoma is seen in serial sections. Summary: Benign prostatic hypertrophy with two areas of recent red infarction (fig. 1)."

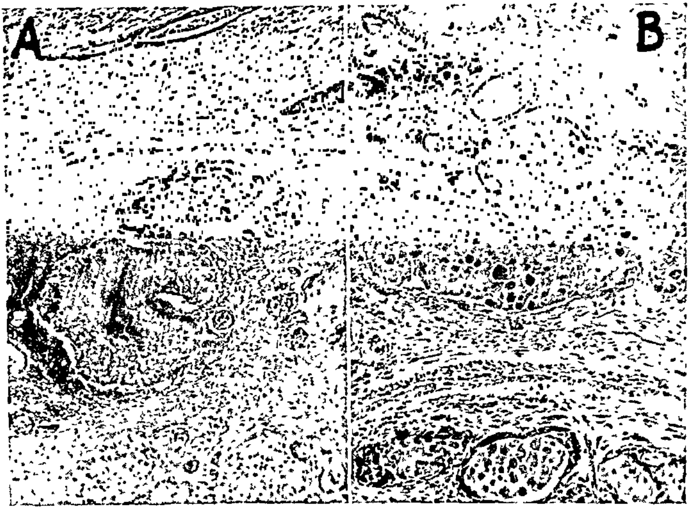

FIG. 1 *A*, low (×65), and *B*, medium power magnification (×100), showing infarction Note essentially normal gland fields on left with partial necrosis in middle, and complete necrosis of glands on extreme right

Forty-eight hours after operation, the serum phosphatases were again determined on fasting blood samples which showed no hemolysis. The total acid phosphatase was 4 3 units per 100 cc, the formalin resistant 3.2 and the alkaline phosphatase 10.4 units per 100 cc. Another sample was also examined simultaneously by the routine biochemical laboratory which reported the following findings: Total acid phosphatase 3.4 units per 100 ccs and alkaline phosphatase 6.0 units per 100 ccs.

The patient made a satisfactory and uneventful recovery and was discharged on September 4th, 1948.

NOTE ON THE TERM FORMALIN RESISTANT ACID PHOSPHATASE

In addition to the total acid phosphatase we have also measured the formalin resistant phosphatase. This procedure was introduced by Abul Fadl and King[1] as an aid in distinguishing prostatic acid phosphatase from the other acid phosphatases which may appear in the serum under certain conditions. This subject has recently been reviewed by King and Delory[5] but some reference to it may be given here. There are probably several enzymes in the acid phosphatase group and there are at least two (other than that elaborated in the prostate) present normally in blood. One of these is found in the red cells and may be liberated by hemolysis while another is normally present in the sera of both men and women. These enzymes differ in their behaviour with formalin which completely destroys the red cell enzyme, partially destroys the normal plasma acid phosphatase, but has no effect on the prostate enzyme. The use of formalin therefore has a double advantage: 1) It eliminates the falsely high results which may be obtained from hemolysed serum; and 2) it provides evidence of *the origin of the acid phosphatase* which has led to the high serum level in a particular set of circumstances.

DISCUSSION

The interesting feature of this case was the extremely high prostatic phosphatase found 12 hours after admission and the fall to within normal limits after operation.

Both results were confirmed independently as already mentioned, using slightly different procedures: for acid phosphatase an acetate buffer was used instead of the citrate buffer employed by us, while the alkaline phosphatase was determined by the original King and Armstrong method[5] whereas we used a later modification.[6,7]

The basis for the high serum levels of acid phosphatase in metastatic prostatic carcinoma was established by Gutman, Sproul and Gutman[8] in 1936 who detected the enzyme at the site of the skeletal metastases secondary to carcinoma of the prostate. Gomori[9] developed histological techniques for the demonstration of the phosphatases in tissues and showed the presence of acid phosphatase in the prostatic epithelium where it is apparently produced. The presence of the prostatic acid phosphatase in the blood, is dependent partly on the invasion of blood and lymph channels by malignant tissue and partly on the rate of production of phosphatase by the prostatic tumor.[10]

Several studies have been made of prostatic infarction, for example that of Rogers,[11] and the earlier review of Hubly and Thompson.[12] Some of the cases studied were proved to be caused by catheter trauma as seemed to be the case in the patient we are considering here, but there is no record of associated phosphatase determinations.

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[5] King, E. J. and Delory, G. E.: Postgrad. Med. J., **24:** 299, 1948.

[6] King, E. J. and Armstrong, A. R.: Can. Med. Assoc. J., **31:** 376, 1934.

[7] King, E. J., Haslewood, G. A. D. and Delory, G. E.: Lancet, **1:** 886, 1937.

[8] Gutman, E. B., Sproul, E. E. and Gutman, A. B.: Am. J. Cancer, **28:** 485, 1936.

[9] Gomori, G.: Arch. Path., **32:** 189, 1941.

[10] Sullivan, T. J., Gutman, E. B. and Gutman, A. B.: J. Urol., **48:** 426, 1942.

[11] Rogers, W. C.: J. Urol., **57:** 584, 1947.

[12] Hubly, J. W. and Thompson, G. J.: J. Urol., **43:** 459, 1940.

The present findings could be explained on the assumption that the prostatic phosphatase was able to pass into the blood stream through the freshly infarcted areas. Such a possibility, namely, that operative or catheter trauma might temporarily open up communication between the prostatic cells and the general circulation is mentioned by Herbert[13] although she reports no case of such an incident.

If the suggested hypothesis is the true explanation of our findings, then the level of the serum acid phosphatase would probably be dependent on the extent of the infarction. Furthermore, the level at any time is probably the resultant of the rate of liberation of the enzyme into the blood stream and its rate of destruction.[13] Consequently, the serum acid phosphatase concentration found, in a case such as we have described here, would probably also be dependent upon the time elapsing between the development of the infarct and the withdrawal of the blood for analysis.

SUMMARY

A case is reported of a 72 year old man who had suffered recent trauma to his prostate in situ and in whom the serum acid phosphatase was extremely high preoperatively.

Following suprapubic enucleation, the serum acid phosphatase returned to normal limits.

The presence of recent infarcts in a benign hypertrophy of the prostate was found on histological examination.

The significance of the raised phosphatase value is discussed.

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[13] Herbert, F. H.: Quart. J. Med., 59: 221, 1946.

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THE CHOICE OF OPERATIVE APPROACH FOR PROSTATECTOMY[1]

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The comparison of different methods of prostatectomy is a provocative subject which for many years has occasioned endless discussion and controversy. Recently Dr. David M. Davis[2] emphasized that the time has come to stop advocating certain types of prostatectomy because one can approach the prostate safely and accurately from each direction. "As our opportunities increase, our responsibilities increase, and I particularly call upon you young men not to let anybody, regardless of who he is, persuade you that you can neglect any one of these avenues of approach to the prostate. You must master them all,—every one of them." Dr. Davis has thus expressed the necessary and progressive attitude which we should accept in our approach to prostatic surgery.

The individual surgeon is likely to develop favorite methods of prostatectomy which seem to attain the goal of low mortality and morbidity and which therefore become predominant in his practice. In the majority of cases of benign prostatic hyperplasia any one of four operative approaches may be used, depending on the ability of the surgeon, the preoperative and postoperative care, and the available anesthesia. However, it is a fact that no one method of prostatectomy is applicable to all cases. Thus for example, cancer of the prostate, a disease which is appallingly common, cannot be totally extirpated by the transurethral route. Nor is it possible to deal properly with a large diverticulum of the bladder in the course of a perineal prostatectomy. These are simple facts which even the most rabid advocate of either of these methods cannot deny. However, to define the precise indication for each of the four methods of prostatectomy is not a matter on which urologists find easy agreement. The following study of 200 consecutive prostatectomies was undertaken in an effort to elucidate and clarify this problem.

In this consideration of the selective management of prostatism a survey of the conditions present in each patient which determine preoperative preparation, method of operation and postoperative care will be given. The complications pursuant to each type of operation and the duration of hospitalization will be shown in detail.

Table 1 shows the age distribution and the type of operation chosen in this group of 200 consecutive patients undergoing prostatectomy. In no instance was age alone a determining factor in selecting the type of operation employed. Only 4 operations were performed on patients under the age of 50 and only 31 or 15.5 per cent were performed on patients under the age of 60, whereas 161 or 80.5 per cent were performed on patients between the ages of 60 and 80. No patient was refused operation and there were 8 or 4 per cent operated upon between the ages of 80 and 90 years without a fatality. The general age distribution of any group may be a reflection of hospital population and will vary locally and geographically within limits. It is apparent that transurethral and perineal prostatectomy were employed more frequently than suprapubic and retropubic prostatectomy for each decade; it will be of interest to compare this operative incidence with subsequent results as greater experience is gained with each method especially the retropubic. If the suprapubic and retropubic are added it is seen that 54 or 27 per cent were operated by the transabdominal route as over against 34.5 per cent transurethral and 38.5 per cent perineal prostatectomy. There were 2 deaths in the group which occurred in patients in the eighth decade; one was due to coronary thrombosis and cardiac failure 30 days after transurethral prostatectomy for inoperable carcinoma of the prostate, and the other was owing to septicemia and endocarditis 22 days after suprapubic prostatectomy for benign hyperplasia. Death in the former case was a sudden unpredictable event. In the latter case in retrospect it is our opinion that inadequate preoperative preparation was an important factor in the complicating sepsis which resulted in the fatal outcome.

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[1] Read at annual meeting. Northeastern Section, American Urological Association, Seigniory Club, Quebec, October 13–15, 1948.

[2] Millin, T.: Retropubic prostatectomy. J. Urol., 59: 267–280, 1948. Davis, David M.: Discussion of above.

TABLE 1.—*Age distribution and operation for 200 prostatectomies*

AGE	SUPRAPUBIC	RETROPUBIC	TRANSURETHRAL	PERINEAL	TOTAL
years					
Under 50			3	1	4
50–60	4	5	11	7	27
60–70	12	14	20	40	86
70–80	7†	9	32*	27	75
80–90	1	2	3	2	8
Total.......	24	30	69	77	200

* 1 death from cardiac decompensation.
† 1 death from septicemia.

From table 2 it is seen that only 16.5 per cent of patients operated upon had relatively insignificant degrees of urinary retention. Several of these were patients having early carcinoma of the prostate as the indication for operation. In the group of 59 (29.5 per cent) having partial but not total retention of urine there were 13 patients having definite renal insufficiency. This group if not seeking medical advice or if not rendered therapy will become part of the last group of chronic retention culminating in total retention of urine and would ultimately comprise the group with the poorest prognosis; 108 (54 per cent) of 200 patients had total retention of urine at the time of admission to the hospital. Forty-eight of these patients had symptoms and signs of renal insufficiency as well as chronic retention of urine and 60 (30 per cent) represented the balance of fairly sudden onset of acute total retention often precipitated by an intercurrent event not directly related to the prostate, e.g. operation, alcoholism, cardiac accident, traumatic injury, or acute febrile illness. Hemorrhage was a precipitating factor for retention and hospital admission in 20 cases (10 per cent). Symptoms of urinary infection accompanied by pyuria were prominent in 89 (44.5 per cent) patients.

Other conditions simultaneously present or antedating prostatic difficulties are of especial significance in the general management as well as the operative approach to the prostate. These have been tabulated and are shown in table 3.

TABLE 2

Incidence of urinary retention		
Residual urine less than 100 cc	33	(16.5%)
Partial retention more than 100 cc	59	(29.5%)
Total not having complete retention	92	(46%)
Total acute retention of urine	60	(30%)
Chronic retention of urine (total)	48	(24%)
	108	(54%)
Incidence of azotemia, infection and hematuria		
Renal insufficiency	61	(30.5%)
Symptoms of infection with pyuria	89	(44.5%)
Gross hematuria	20	(10%)

TABLE 3.—*Concomitant conditions present affecting management*

	CASES
Cardiac disease	50
Hernia	45
Pernicious anemia	7
Chronic bronchitis	7
Diabetes mellitus	7
Gastric carcinoma or ulcer	5
Carcinoma of colon	5
Varicose veins	5
Secondary anemia severe	4
Cholelithiasis	3
Cirrhosis of liver	3
Fracture of femur	2
Pulmonary tuberculosis	2

Each of these conditions requires particular consideration and treatment during the preoperative and postoperative periods. In addition each may alter the method of operative approach according to the demands imposed by its inherent characteristics and need for either medical or surgical therapy. There were 50 patients (25 per cent) having definite cardiac disease either in the form of coronary thrombosis (15 per cent) or frank cardiac decompensation (10 per cent). It has been shown that these patients tolerate surgery well if given adequate preparation first[3] and aside from unpredictable accidents which will occur spontaneously without surgery, can be expected to recover satisfactorily. Choice of anesthesia and operation is determined by such factors as necessary position on the table, nature of the local lesion, exercise tolerance, vital capacity, skeletal deformities, presence of infection, hypertension, and vascular disease. It is interesting that the method of operative approach for these 50 cardiac patients is found to be as follows:

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[3] Harrison, J. H.: The indications and limitations of prostatic surgery in the presence of cardiac disease. Am. J. Med. Sc., 204: 469–482, 1942.

	Cases
Perineal prostatectomy	25
Transurethral prostatectomy	14
Retropubic prostatectomy	7
Suprapubic prostatectomy	4
	50

Forty-eight of these patients did well; 1 patient died of septicemia and endocarditis after a one stage suprapubic prostatectomy; it was not the operative approach but rather the lack of preoperative preparation which caused this fatality. One patient died of cardiac decompensation and pulmonary edema 30 days after a transurethral prostatectomy. The predominance of perineal and transurethral prostatectomy in this group of cardiac patients is evidence of our confidence that these procedures are well tolerated in the presence of heart disease.

The incidence of hernia (22.5 per cent) was a significant factor in causing a choice of either perineal or transurethral prostatectomy. In a few instances herniorrhaphy was carried out simultaneously with either perineal or transurethral prostatectomy. Likewise other intraabdominal pathological changes demanding surgical intervention seemed an indication for adopting these routes rather than subjecting the patient to another transabdominal procedure. Local conditions of the urinary tract e.g. stricture, calculus, and tumor, gave other special indications for the method of intervention. Chronic pulmonary disease is of special significance with reference to anesthesia as regards diminished vital capacity, atelectasis and complicating pneumonia. Position on the table is limited by skeletal and arthritic deformities at times. It is to be noted that 21 of these patients had undergone prostatectomy previously all for benign hyperplasia originally 2 to 20 years before; 5 of these represented carcinoma of the prostate and 16 were for recurrent benign hyperplasia. It is seen from table 4 that 2 total perineal prostatectomies were carried out for carcinoma after previous suprapubic prostatectomy for benign hyperplasia; 3 transurethral prostatectomies were performed on patients having inoperable carcinoma following 1 suprapubic prostatectomy and 2 perineal prostatectomies done more than 5 years before. This illustrates the importance of continued careful follow-up of patients after prostatectomy for benign hyperplasia and also emphasizes the importance of considering total prostatectomy on selected suspected lesions in the seventh and eighth decades.

It is to be noted from table 4 that of the patients requiring a second operation on the prostate that 10 had had transurethral prostatectomy for benign hyperplasia and that secondary operation was not due to carcinoma. One half of those having had suprapubic prostatectomy previously came in because of carcinoma (3 of 6); 5 had had previous perineal prostatectomy for benign hyperplasia and 2 of these were admitted with inoperable obstructing carcinoma treated by transurethral prostatectomy, orchidectomy and estrogens at this time.

The local conditions listed in table 5 impose certain factors which have affected the choice of operative approach in all cases. The percentage of patients undergoing prostatectomy for carcinoma of the prostate was 19 per cent and this is to be expected from figures seen in table 1 which show that 84.5 per cent of patients were over 60 years of age. It should be emphasized that this does not include those patients admitted during the same period of time who had inoperable carcinoma of the prostate treated only by orchiectomy and estrogens without prostatectomy. The other complicating conditions in table 5 must be taken into consideration and correlated with those in tables 3 and 4 as they are found in the individual patient in arriving at the most desirable operation for that patient.

TABLE 4.—*Previous prostatectomy requiring further surgery*

PREVIOUS OPERATION	SUBSEQUENT OPERATION				
	Suprapubic	Retropubic	Transurethral	Perineal	Total
Suprapubic	1	0	2 (1*)	3 (2*)	6
Transurethral	1	2	3	4	10
Perineal	0	0	5 (2*)	0	5
	2	2	10	7	21

* Carcinoma after previous prostatectomy for benign hyperplasia.

TABLE 5.—*Primary urologic diagnosis*

Benign hyperplasia of prostate	163 (81%)
Carcinoma of prostate	37 (19%)
Total	200

Complications of primary disease

Cystitis, suppurative	89
Renal insufficiency	61
Prostatitis, suppurative	28
Previous prostatectomy	21
Calculus, vesical	8
Calculi, prostatic	6
Stricture of urethra	6
Contracture, vesical outlet	4
Diverticula of bladder	4
Abscess of prostate	2
Ureteral calculus	2
Hydro-ureter and hydronephrosis severe, bilateral	2

In spite of a few authors to the contrary,[4] preoperative preparation is a most important aspect in the management of the patient suffering from prostatism. The implication is not that all should have preoperative drainage of the bladder but rather only those who have retention of urine and/or azotemia.[5] Thanks to the soft gum rubber Foley catheter (16 F) which is relatively non-irritating, drainage of the bladder via the urethra may be carried out in the majority of cases without complication. This catheter with the 5 cc bag is suited admirably to the problem of preoperative drainage in the absence of hemorrhage and blood clots. Avoiding the use of adhesive allows for drainage around the catheter and a diminished incidence of urethritis, prostatitis and epididymitis. The use of the sulfonamides and antibiotics before and after operation have diminished appreciably the incidence of suppurative complications. Positive cultures for Escherichia coli or B. aerogenes was obtained in 66 (33 per cent) cases upon admission. Staphylococci and enterococci were found in 29 and 26 cases respectively. Bacillus proteus 11, hemolytic streptococcus 6, B. pyocyaneus 6 and Salmonella enteritidis 1 constituted the remainder of the organisms found on culture. The implications of the possibilities of chemotherapy and antibiotic therapy to combat these organisms are obvious if adequate preoperative preparation is carried out. Fortunately the members of the colon family comprise the most frequent infecting agents which are the most responsive to the sulfonamides. Likewise it is just as fortunate that B. proteus was present in only 5.5 per cent of cases.

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[4] Walters, G. A. B.: Immediate prostatectomy for retention of urine. Brit. Med. J., 1: 638, 1948.

TABLE 6

	PREOPERATIVE PREPARATION	POSTOPERATIVE
No drainage	70 (35%)	
Constant drainage (urethral)	107 (53.5%)	200 (100%)
Constant drainage (S P.)	23 (11.5%)	26
Sulfonamide therapy	140 (70%)	178 (89%)
Penicillin therapy	24 (12%)	106 (53%)
Streptomycin therapy.	2 (1%)	7 (3.5%)
Transfusion	6 (3%)	
Heparin	2 (1%)	7

In this group of 200 patients as seen in table 6 there were 70 in whom preoperative drainage was not used; in 107 constant drainage via the urethra was employed and in 23 a suprapubic catheter was inserted into the bladder either via a trocar or by open cystotomy under local anesthesia. Preoperative drainage was used for all patients having total retention of urine and partial retention of urine with renal insufficiency. The average period of preoperative drainage for these 130 patients was 8 days. Sulfonamides in the form of sulfadiazine or a combination of sulfadiazine and sulfamerazine in the dose of 2 gm. per day was administered during the preoperative period to 140 (70 per cent) patients; 9 patients exhibited a toxic reaction in the form of dermatitis or fever with leukopenia. Methenamine and calcium mandelate were used chiefly for those patients not tolerating or not receiving the sulfonamides. Penicillin was used preoperatively in 24 cases chiefly where mixed urinary infections were present and streptomycin in 2. Digitalization was necessary and employed for 20 of 50 cardiac patients; preoperative transfusion was given to 6. Heparin was used in 2 cases before operation for phlebothrombosis present at admission and continued until this condition had been adequately controlled. Ambulation and active exercise of the lower extremities was used in all patients as prophylaxis against phlebothrombosis both before and after operation. Prophylactic femoral vein ligation was used in no cases in this group and no deaths occurred from pulmonary embolism.

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[5] Davis, E : The renaissance of prostatectomy with particular reference to minimal hospitalization without preliminary drainage. *J. Urol*, *48: 163–169, 1942.*

In table 7 it is seen that the preoperative diagnosis of benign hyperplasia was made in 163 cases and of carcinoma in 37 instances. In one patient having a retropubic prostatectomy a carcinoma in situ was found by the pathologist. Suprapubic prostatectomy was performed on 1 patient having multiple vesical calculi and an inoperable carcinoma of the prostate. A preoperative diagnosis of operable carcinoma of the prostate was made in 21 cases and total prostatectomy was completed in 18 cases; in 3 instances the process was found to have extended outside of the gland and to be so fixed that total prostatectomy was impossible. In 3 of the 18 cases in whom total extirpation was completed no evidence of carcinoma could be found, though each showed squamous metaplasia and chronic inflammation. Bilateral orchiectomy was performed upon all having carcinoma except one who refused to have this and was sterilized by means of roentgen ray therapy; estrogenic therapy was employed for all. It has seemed to us that removal of the androgenic stimulus insofar as possible as early as possible is indicated in all cases of carcinoma of the prostate. In several cases total prostatectomy was carried out several months after orchiectomy and estrogens had been administered which had caused a striking decrease in size and fixation of the gland. So insidious is the metastatic spread of this tumor it seems that even though total surgical extirpation has been accomplished that the full benefit of hormone therapy should be made available to the individual for his greatest protection in case unknown metastatic spread has already occurred. The policy of withholding orchiectomy until metastases have appeared and are causing symptoms does not seem to be justified or to be effecting the most vigorous attack on cancer of the prostate from the beginning. In 15 cases transurethral prostatectomy was necessary for obstructing inoperable carcinoma which had not responded sufficiently locally as a result of orchiectomy and estrogens to permit emptying the bladder. In 1 case where there was a coincident grade 4 papillary carcinoma of the bladder and also a separate carcinoma of the prostate, simul-

TABLE 7.—*Correlation of preoperative diagnosis and operation employed*

	SUPRAPUBIC	RETROPUBIC	TRANS-URETHRAL	PERINEAL	TOTAL
Benign hyperplasia	23*	30	54	56	163
Carcinoma	1	0	15*	21†	37

* 1 death occurred after operation.

† 3 were inoperable carcinoma; 3 were not carcinoma; 18 were total prostatectomies.

taneous bilateral ureterosigmoidostomy and perineo-abdominal total cystectomy were carried out.

In the evaluation of the results obtained an analysis of the days of postoperative drainage, the days in the hospital after operation, and the postoperative complications has been made. These are illustrated in tables 8 and 9.

TABLE 8.—*Postoperative hospitalization average*

	SUPRAPUBIC	RETROPUBIC	TRANS-URETHRAL	PERINEAL	TOTAL
Days C.D.	9	7	5	8	
Days to discharge	16	16	14	18	
14 days or less (107)	54%	60%	62%	42%	53.5%
15–21 days (55)	33%	23%	20%	34%	27.5%
22–28 days (21)	8%	6%	10%	13%	10.5%
Over 29 days (17)	4%	10%	7%	10%	8.5%
Total 200					100%

TABLE 9.—*Postoperative complications*

	SUPRAPUBIC	RETROPUBIC	TRANSURETHRAL	PERINEAL	TOTAL
No complications	13 (54%)	14 (47%)	38 (55%)	50 (65%)	115 (57.5%)
Hemorrhage (clots evacuated)	1 (4%)	3 (10%)	6 (8.7%)	3 (3.9%)	13 (6.5%)
Hemorrhage (cystotomy)	1 (4%)	1 (3.3%)	2 (2.9%)	4 (5.2%)	8 (4%)
Hyperpyrexia (102F)	5 (20%)	6 (20%)	14 (20.3%)	6 (7.8%)	31 (16.5%)
S.D. reaction	2	2	2	3	9
Epididymitis*	0 (0)	2 (6.6%)	3 (4.3%)	6 (7.8%)	11* (5.5%)
Phlebothrombosis	1 (4%)	0 (0)	2 (2.9%)	6 (7.8%)	9 (4.5%)
Pulmonary infarction	0 (0)	0 (0)	1 (1.4%)	3 (3.9%)	4 (2%)
Wound infection	3 (12.5%)	2 (6.6%)		4 (5.2%)	9 (4.5%)
Fistula P.O. temporary	2	2	0	4	8
Incontinence	0 (0)	0 (0)	4 (5.8%)	5† (6.5%)	9 (4.5%)
Atelectasis	2 (8.3%)	2 (6.6%)	2 (2.9%)	1 (1.3%)	7 (3.5%)
Cardiac failure	2 (8.3%)	1 (3.3%)	3 (4.3%)	0 (0)	6 (3%)
Coronary thrombosis	0 (0)	1 (3.3%)	1 (1.4%)	1 (1.3%)	3 (1.5%)
Septicemia	1 (4.1%)	0 (0)	0 (0)	1 (1.3%)	2 (1%)
Anuria	0 (0)	0 (0)	1 (1.4%)	0 (0)	1 (0.5%)
Death	1 (4.1%)	0 (0)	1 (1.4%)	0 (0)	2 (1%)
Total of operations	24	30	69	77	200

* 66 patients had vasectomy and 3 epididymitis; 134 patients did not have vasectomy and 8 had epididymitis.

† 2 total prostatectomy.

The average number of days of constant drainage of the urinary bladder after operation was less after transurethral prostatectomy than any other method (table 8) (5 days); this method was followed by the retropubic (7 days), perineal (8 days) and suprapubic (9 days). The time to remove the catheter is an arbitrary one and will vary with the individual surgeon. The average days in the hospital after operation were shortest also after transurethral prostatectomy (14 days) and longest for perineal prostatectomy (18 days) with suprapubic and retropubic coming in between (16 days each). Too much cannot be construed from these figures with regard to the merits of the type of operation except as a general indication of what can be expected for a group of patients at this age with the accompanying types of pathological changes present and the complications likely to occur. For each group this seems rather a long time for hospitalization after prostatectomy; however, this impression is improved on consideration of the fact that 107 patients were discharged in 2 weeks or less after operation and that only 17 were hospitalized for longer than 4 weeks. The most common causes of prolonged hospitalization were postoperative urinary incontinence, debility and cardiac disease. From table 8 it may be pointed out that 59 patients having perineal prostatectomy were discharged in less than 3 weeks (76 per cent) and 33 (42 per cent) were discharged in 2 weeks or less. Fifty-seven transurethral prostatectomies (82 per cent) were discharged in less than 3 weeks and 43 (62 per cent) left the hospital in less than 2 weeks. Likewise 18 (60 per cent) patients having retropubic prostatectomy were discharged in less than two weeks and 25 (83 per cent) in less than 3 weeks; at the same time it is seen that for the suprapubic prostatectomies 13 or more than 50 per cent were discharged in less than 2 weeks and 21 (87 per cent) were discharged in less than 3 weeks. The average postoperative hospitalization for the 200 patients was 16 days.

The major postoperative complications are shown in table 9 according to the type of operation performed. The serious complication of urinary incontinence occurred 4 times after transurethral prostatectomy; one of these was an inoperable carcinoma of the prostate; a perineal plastic was performed in an attempt to cure this condition in 3 patients. Incontinence was cured for 1, improved for 1 and not improved for 1. Bilateral ureterosigmoidostomy was performed for this third patient with complete cure of incontinence followed by an afebrile convalescence and return of the patient to an active existence. This is a radical measure but the incapacitation accompanying total incontinence warrants radical measures for cure. The pattern for this has been set by the pediatric surgeon in the cure of exstrophy of the bladder. Four instances of incontinence were after total perineal prostatectomy for carcinoma (3 cases) and suspected carcinoma (1 case) and 1 after simple enucleation for benign hypertrophy. Temporary incontinence after retropubic prostatectomy cleared completely within 1 month in 2 cases.

Acute epididymitis occurred 11 times concomitant with postoperative urethral catheter drainage. Of 66 who had vasectomy, there were 3 with epididymitis and of 134 without vasectomy, 8 had epididymitis. Acute epididymitis occurring after vasectomy was due, we believe, to previous constant drainage via a urethral catheter. This is an incidence of 5.5 per cent of postoperative acute epididymitis which is relatively small when one considers that urinary infection was a prominent finding in 44.5 per cent of patients at the time of admission to the hospital. It is significant that preoperatively 140 (70 per cent) patients received sulfonamides, 24 (12 per cent) penicillin and 2 (1 per cent) streptomycin; postoperatively

178 (89 per cent) were treated with sulfonamides, 106 (53 per cent) penicillin, and 7 (3.5 per cent) streptomycin. Toxic reaction in the form of fever, rash, and leukopenia due to sulfonamides occurred in 9 patients. In each, recovery ensued with cessation of the drug. Phlebothrombosis occurred 9 times and was treated successfully with heparin in each case even though 4 of these had pulmonary infarction causing the initial symptoms. Postoperative hyperpyrexia (102F) exclusive of drug reaction occurred in 31 (15 per cent) patients; the highest incidence was after transurethral prostatectomy 20 per cent and retropubic prostatectomy 20 per cent. Atelectasis was a significant complication in only 8 (3.5 per cent) of cases. Eight (4 per cent) patients had temporary urinary fistulas all of which healed completely before discharge from the hospital and in less than 1 month except in 1 patient who had a perineal cellulitis after total prostatectomy causing drainage for 6 weeks. There were no rectal or rectourethral fistulas. Wound infection occurred in 9 of the open operations (131) or 6.8 per cent; the incidence of wound infection in transurethral prostatectomy is difficult to ascertain but is thought to be high if judged on the basis of postoperative pyuria. Twenty-one patients (10.5 per cent) had complicating postoperative hemorrhage; 13 (6.5 per cent) were not severe and were managed by irrigation and evacuation alone; 9 (4.5 per cent) required postoperative cystotomy. Cardiac decompensation occurred in 6 and coronary thrombosis in 3 during the postoperative period. One of the latter was fatal and another patient having arteriosclerotic heart disease died of septicemia. One patient was anuric for 5 days after transurethral prostatectomy and recovered. It is to be noted that 115 (57.5 per cent) of patients had no postoperative complications and that these constituted approximately 50 per cent of the suprapubic, retropubic and transurethral prostatectomies whereas 65 per cent of perineal prostatectomies had no complications.

From a consideration of the foregoing data, it can be concluded that a low mortality rate (1 per cent) can be attained using all methods of prostatectomy by applying these methods to selected cases. It is shown that age per se is no contraindication to carrying out radical surgery. The mortality rate today from cancer of the prostate is forbidding and its incidence is appalling (estimated at 14[6] to 29 per cent[7] of males over the age of 50). Efforts are being made by only a few to attack this problem in a realistic manner.[8] There is only one cure for cancer of the prostate today and that is total prostatectomy. Orchiectomy and estrogenic therapy yield dramatic results that are magnificent palliation for which we owe thanks to the monumental work of Huggins.[9] Hinman[8] has estimated that only 5 in every 100 patients with cancer of the prostate are seen early enough to justify a total radical procedure. To correct this situation calls for education of the laity as well as ourselves in order to make the diagnosis early enough. If it is true that more than 3 million men in this country today have cancer of the prostate,[8] then the efforts to cure this disease by radical surgery have been practically negligible. The best results will be obtained if we make an earnest effort to fit the therapy to the patient rather than attempting to make the patient conform to our pattern of surgery. By any approach the fundamental surgical principles continue to be of paramount importance namely, preoperative preparation, position, exposure, illumination, hemostasis, asepsis, drainage, chemotherapy, proper anesthesia, and postoperative care.

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[6] Rich, A. R.: On the frequency of occurrence of occult carcinoma of the prostate. J. Urol., 33: 215–223, 1935.

[7] Kahler, J. E.: Carcinoma of the prostate gland; pathologic study. J. Urol., 41: 557–574, 1939.

[8] Hinman, F.: The obstructive prostate. J. A. M. A., 135: 136–141, 1947.

[9] Huggins, C.: Prostatic cancer treated by orchiectomy: The five year results. J. A. M. A., 131: 576–581, 1946.

The following discussion will summarize the indications and contraindications for each method of prostatectomy in following a policy of selective management of prostatism. The major premise of this discussion will be to fit the operation to the patient rather than to fit the patient to our individual pattern of surgery. It is unquestionable that there is a definite place for each type of prostatectomy and that universal efforts should be made to perfect the technique of each.

SUPRAPUBIC PROSTATECTOMY

Suprapubic prostatectomy is the easiest method to master and uniformly gives good end results for benign hyperplasia. It carries a somewhat higher mortality rate apparently due to its being both a transabdominal and transvesical procedure which involves more visceral traction and the opening of more tissue planes into which potential sepsis may supervene. The transabdominal approach per se is likely to interfere with vital capacity to a greater extent than is the transurethral or perineal method. We have considered the contraindications to the abdominal approach to be extreme obesity, severe cardiac or pulmonary disease, general debilitation of the patient, inguinal or ventral hernia, a recent abdominal operation for other disease or the necessity for the same to be performed, abscess of the prostate, carcinoma of the prostate, and fibrous contracture of the vesical neck. Our indications for suprapubic prostatectomy have corresponded closely to those of Higbee[10] and of many others.[11, 12] The operation permits the adequate simultaneous treatment of coexisting, intravesical pathological changes, avoidance of trauma to the rectum, and produces the least disturbance of sphincteric and genital functions. It has the advantage of providing for both suprapubic and urethral drainage, if necessary. It has been employed by us chiefly for those cases having vesical calculi, large diverticula of the bladder, excessive intravesical enlargement of the prostate and coexistent vesical neoplasm. Careful consideration regarding the advisability of total cystectomy is given the latter. It is common experience that open enucleation of the large prostate is preferable to transurethral prostatectomy. Where there is encroachment upon the ureters by a subtrigonal hyperplasia enucleation under direct visualization is desirable. The fact that previous suprapubic drainage has been necessary in preparation for prostatectomy has not in itself been considered a necessary indication for suprapubic prostatectomy. The choice of operation is determined by consideration of all the characteristics of that individual patient. The presence of skeletal deformities which prevent putting the patient in a proper position for either transurethral or perineal prostatectomy may be an indication for transabdominal prostatectomy.

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[10] Higbee, D. R.: The status of perineal prostatectomy today. J. A. M. A., 139: 141–144, 1949.

[11] Quinby, W. C. and Landsteiner, E. K.: Hemostasis by thrombin and fibrin foam in suprapubic prostatectomy; an analysis of 40 cases. New England J. Med., 235: 609–612, 1946.

[12] Joelson, J. J.: Personal communication.

RETROPUBIC PROSTATECTOMY

This relatively new approach to the prostate developed by Millin[2] has caused much discussion and few have yet had sufficient experience with this method of approach to permit final evaluation of the advantages as well as the disadvantages. There are certain obvious anatomic and physiologic advantages to this direct abdominal extravesical approach to the prostate gland. The outstanding feature of the operation is that the bladder is neither opened nor disturbed during the enucleation and accurate visualization of the prostatic bed and vesical outlet can be obtained following removal of the prostate. Hemostasis can be accomplished under direct vision by suture and electrocoagulation. The operation has been attended by few complications and is characterized by a smooth, comfortable postoperative course in most cases. The urethral catheter drains the uninjured urinary bladder and is less interfered with by any bleeding in the prostatic bed because the prostatectomy has been extravesical rather than transvesical. If there are intravesical pathological changes that need attention, the transvesical approach is indicated rather than the extravescial or retropubic approach. Because it is an abdominal aperation there are similar contraindications to it as for suprapubic prostatectomy, such as abscess, cancer, fibrosis of the vesical neck and extreme obesity. The attempt at enucleation of the small adherent prostate and contracted vesical neck meets the same difficulties by this approach as by the transvesical approach. When suppurative prostatitis or abscess of the prostate is present, infection of the prevesical space with postoperative drainage and urinary fistula as well as osteitis pubis is courted by the retropubic approach. The large benign glands are easier for enucleation by this technique; however, the anatomic distribution of the hyperplasia is of importance and the retropubic approach is more difficult for the distinctly subtrigonal, posterior and excessive intravesical enlargement. This approach has the advantage of being less likely to cause disturbance of sphincteric and genital functions. It is necessary at times to excise a wedge of the vesical neck to prevent postoperative stricture therein. Millin and others have performed total prostatectomy by this approach for cancer of the prostate. However, our experience indicates that this is not the most desirable or direct approach for radical prostatectomy. This experience is based on total prostatectomy via the perineum, retropubic enucleation for benign hyperplasia and the use of the retropubic approach to total cystectomy with prostatectomy and vesiculectomy. For the latter operation it was found that the combined perineo-abdominal approach definitely facilitates the delivery of the prostate, vesicles and bladder.

TRANSURETHRAL PROSTATECTOMY

Transurethral prostatectomy has enjoyed a greater numerical popularity than any other operative method in this country. Technically it is the most difficult procedure to learn because it is an indirect approach with the greatest visual and palpatory limitations. It has the disadvantage of being a closed operation with the least provision for drainage of any method. It is ideally adapted to the relief of obstruction by the small fibrous gland or median bar, median lobe enlargement, contracture of the vesical outlet, small adenomatous hyperplasia which is not subtrigonal, and for the inoperable neoplastic prostate causing obstruction which has not responded to orchiectomy and estrogenic therapy. With control of infection and good hemostasis it yields good results with a low mortality rate. For the majority of surgeons it is not the method of choice for removal of large glands. It has the advantage in the case of severe cardiac patients that they may be operated upon under low spinal, caudal or general anesthesia in a comfortable position in spite of orthopnea and be little disturbed by the operation. Catheter drainage is necessary for only 2–3 days after operation in most cases and the days in the hospital after operation are less than for any other method. On the other hand the morbidity is higher, repeated operations more often necessary, urinary infection more prolonged and the functional result less perfect than when an open surgical enucleation is carried out. It is an ideal operation fo appropriately selected cases. It is specifically of value for the cord bladder with contracted vesical neck and hypotonic bladder after abdomino-perineal resection for carcinoma of the rectum. It overcomes the disadvantages of transabdominal prostatectomy for most contraindications except carcinoma and infection. It is not desirable for the patient having hydro-ureter and hydronephrosis. Severe hemolytic reactions can be avoided by using 3 per cent dextrose instead of distilled water as an irrigating medium. We have used this for 2 years without operative difficulty or postoperative reaction. The hemolytic reaction following the use of distilled water has caused anuria in a small number of patients reported in the literature and probably in a larger number not reported. Urinary incontinence occasionally occurs as a complication of transurethral prostatectomy as a result of an inadequate removal of tissue or when damage occurs to the vesical outlet resulting in a cicatrized funnel shaped opening which is adherent and cannot close. Resection of the apical masses may be followed by paralysis of the external sphincter which causes poor control and dribbling but not total incontinence. Stricture of the urethra has occasionally been a delayed postoperative complication. Impotence is seldom a complication of a carefully performed transurethral prostatectomy.

PERINEAL PROSTATECTOMY

Perineal prostatectomy has not enjoyed the popularity of the above three procedures for several reasons.[10] Draper[13] has shown that in one large hospital perineal prostatectomy was done in only 81 cases in a period of 27 years and 12 of these were done in 1946. This operation, originally perfected by Dr. Hugh Young, has undergone various modifications but has enjoyed frequent usage in the hands of relatively few surgeons. Higbee[10] has very aptly attributed this unpopularity to a lack of knowledge of the anatomy of the male perineum, absence of teaching of the method and the hazards of injury to the rectum and structures traversing the triangular ligament. It is our conviction that the method should be taught and that in so doing the magnitude of hazards will be greatly diminished. It is the most direct surgical approach to the prostate gland and is of particular value in those cases wherein the presence of carcinoma is suspected. The prostate can be exposed via the perineum through a small incision which places no burden on vital functions and is ideal for poor risk patients. Extreme extension of the presenting perineum by sharp flexion of the thighs upon the trunk is of utmost importance in obtaining the necessary position. Occasionally deformities of the spine, ankylosis of joints or fractures may make it impossible to obtain a position for this operation and result in the choosing of another method of approach. The davis perineal elevator[14] can be fitted to any standard operating table and has allowed us since its adoption to place the patients who are the poorest risks in proper position for perineal prostatectomy. Evidence of early carcinoma of the prostate is a direct indication for this approach for it is by this method that total radical prostatectomy may be most easily performed and herein lies the only hope of cure for this condition. The predominance of cancer in the seventh decade and over makes one think more frequently of the necessity of this approach, particularly with the ever increasing longevity of the times. When prostatic hyperplasia is great and especially a posterior enlargement the perineal route is easiest because of displacement of the rectum posteriorly and away from the line of incision. When the gland is large and the patient is obese and has other contraindications to an abdominal approach we have found this to be the method of choice. Suppurative prostatitis, abscess of the prostate and prostatic calculi are ideally managed via this route. The patient who has recently had a coronary thrombosis or cardiac decompensation, who has a large obstructing prostate tolerates perineal prostatectomy better than any other method of operation. However, if there are intravesical pathological changes to be remedied simultaneously, the perineal route should not be used. When the technique has been learned, this operation fails to disturb the patient's vital functions and there is little blood loss in the majority of cases. It is, therefore, especially suited for the poorer risks. The method does carry with it a greater risk of rectal injury, postoperative incontinence and impotence than any other approach. The first two complications may be prevented with proper care to anatomical detail; the latter is a real hazard in relatively few of the cases chosen for this approach on account of age and general condition. It is not the operation of choice for the young patient. It is significant that there were no deaths in this group of 77 perineal prostatectomies and particularly so when one considers that 18 of these were total prostatectomies. The approach to surgery of the prostate today must not neglect the curability of cancer when the diagnosis is established early. Colston[15] has reported 48.6 per cent cured, and Hinman[16] 56 per cent cured of cancer of the prostate by radical extirpation in those cases discovered early enough to be thought of as potentially curable by surgery.

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[13] Draper, J. W.: Twenty-seven years of prostatic surgery at Bellevue hospital. Surgery, 23: 515, 1948.

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[14] Designed by E. M. Davis, M.D. and manufactured by C. E. Balbach, Omaha, Neb.

[15] Colston, J. A. C.: Surgical removal of cancer of the prostate gland: Radical operation. J. A. M. A., 127: 69-72, 1945.

[16] Hinman, F. and Hinman, F. Jr.: The early diagnosis and radical treatment of prostatic carcinoma. Read before meeting of California State Medical Association May 1, 1947.

SUMMARY

An analysis has been made of 200 consecutive prostatectomies performed in a teaching hospital where a policy of selective operative approach is practiced. The preoperative preparation, postoperative care, mortality and postoperative complications encountered have been given. The advantages, disadvantages, indications and contraindications for each type of prostatectomy have been discussed. It is emphasized that each method of approach has a definite place in the therapeutic armamentarium. Multiple conditions which must be considered in the individual patient in determining the method of operative approach have been analyzed in detail in 165 instances of benign hyperplasia and 35 of carcinoma of the prostate. There was a mortality rate of 1 per cent in this group of patients. It is concluded that in the approach to prostatic surgery today the operation chosen should be that most suitable for the condition of the individual patient.

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TRANSURETHRAL PROSTATIC RESECTION: A COMPARISON OF TWO SERIES OF CASES[1]

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Almost twelve years ago, one of us (A. H. G.) presented an analysis of 100 consecutive transurethral resections on the prostate gland which he had performed during the preceding 1½ years. It is of interest to inquire as to the progress, or lack of it, which has been obtained in connection with this operation since that time. Therefore, a second series of 100 consecutive cases treated transurethrally was studied with view to making possible comparisons. This second series was operated upon during the period June 1, 1947 to January 1, 1948.

AGE DISTRIBUTION

The average age of all patients operated on transurethally for prostatic obstruction remains at about 70 years (table 1). It should be observed, however, that the age distribution has undergone a change. About twice as many patients are being resected in the 81 to 90 year age group and in the 51 to 60 year age group today as compared with the situation 12 years ago. There is, therefore, a spreading out of the ages at which resection is undertaken; produced on the one hand by a general increase in the old age population, and on the other hand by a tendency to have patients seek urological help at an earlier age. The largest number of cases are now found in the 61 to 70 age group as against the peak in the 71 to 80 age group previously.

PREOPERATIVE CARE AND COMPLICATIONS

Apparently due to the tendency to have patients seek urological help sooner we are now seeing less complicated cases (table 2). While in the first series 31 patients were completely obstructed when first seen, only 16 in the second series had this complaint. Also, in the first series 24 cases had elevation of the nonprotein nitrogen while only 8 in the second series had this complication. Oddly enough, the incidence of large diverticula remains at 5 to 7 per cent.

The resection of recurrent cases remains at 8 to 9 per cent. While the number of resections for recurrent benign growths decreases, the cases of prostatic carcinoma live longer on estrogenic therapy and more carcinomatous local recurrences need resection.

Preoperative hospitalization has decreased slightly (table 4). While the average preoperative stay was 3½ days 12 years ago, it is now 2½ days. Again, this reflects the fact that we are seeing less advanced and less complicated cases.

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[1] Read at annual meeting, Wisconsin Urological Society, LaCrosse, Wis., April 24, 1948, and also at first annual meeting of Southwestern Surgical Congress, Houston, Texas, September 27, 1949.

TREATMENT

The introduction of the routine administration of sulfonamides as well as the invention of the bag catheter have brought about a change in our preoperative care. All patients except those with gross elevation of the nonprotein nitrogen are started on small doses of sulfadiazine on admission. At the same time those with large amounts of residual urine or acutely obstructed are placed on catheter drainage with a No. 16, 5 cc bag catheter. They may be carried along this way for several days while necessary preoperative studies are made. Penicillin or other antibiotics are not used except for some special consideration.

TABLE 1.—*Age groups*

200 cases of prostatic obstruction

AGE GROUPS	100 CONSECUTIVE CASES TREATED BY TRANSURETHRAL RESECTION—JUNE 1, 1935 TO AUGUST 1, 1936	100 CONSECUTIVE CASES TREATED BY TRANSURETHRAL RESECTION—JUNE 1, 1947 TO JANUARY 1, 1948
Average age	69¾ years	70½ years
Eldest case	90 years	89 years
Youngest case	33 years (median bar)	42 years (median bar)
Age groups:		
81–90	8 cases	15 cases
71–80	44 cases	33 cases
61–70	41 cases	37 cases
51–60	6 cases	12 cases
41–50	0 cases	3 cases
31–40	1 case	0 cases

TABLE 2.—*Preoperative findings*

	SERIES 1	SERIES 2
Completely obstructed on admission	31 cases	16 cases
Elevated N.P.N. (36 mg. % or higher):		
Without symptoms	Not given	4 cases
With symptoms	24 cases	4 cases
Recurrent cases	8 cases	9 cases
Adenomata	6 cases	4 cases*
Carcinoma	2 cases	5 cases
Papillomata	2 cases	1 case
Diverticula	7 cases	5 cases
Urinary calculi:		
Ureter	2 cases	0 cases
Bladder	*4 cases*	*6 cases*

* One done elsewhere. One with alkaline incrustations.

Probably because of the ease and safety with which catheter drainage can now be carried out, the number of such cases has increased from 21 per cent to 28 per cent in spite of the above noted decreases in patients acutely obstructed or with high nonprotein nitrogen determinations (table 3). Of the 28 per cent, 3 cases had drainage instituted before admission to the hospital and 25 cases had catheters placed after admission. Only 1 patient in the current series had a suprapubic cystostomy; this was done to remove a large bladder calculus. Three suprapubic cystostomies were done in the series 12 years ago.

TABLE 3.—*Treatment*

	SERIES 1	SERIES 2
One resection	82 cases	92 cases
Two resections	14 cases	6 cases
Three resections	1 case	2 cases
Four resections	3 cases	0 cases
Cystostomy	3 cases	1 case
Catheter drainage (preoperative)	21 cases	28 cases
No drainage (preoperative)	76 cases	71 cases

TABLE 4.—*Hospitalization*

	SERIES 1	SERIES 2
Hospitalization		
Preoperative:		
Average	3½ days	2½ days
Shortest	0 days	0 days
Longest	40 days	20 days
Postoperative:		
Average	10½ days	8⅓ days
Shortest	2 days	3 days
Longest	69 days	56 days
Total hospitalization:		
Average	13¾ days	11 days
Shortest	3 days	3½ days
Longest	63 days	60 days

Ninety-two cases in this recent series had 1 resection, while 6 cases had 2 resections and 2 cases had 3 resections. This compares with 82 cases with 1 resection, 14 cases with 2 resections, 1 case with 3 resections, and 3 cases with 4 resections 12 years ago.

POSTOPERATIVE CARE

In comparing the postoperative reactions in our two groups, one must consider that on one hand we now have the aid of the sulfonamides and penicillin, formerly not available, while on the other hand we now produce a much larger wound area for the absorption of bacteria and products of tissue destruction.

It may be said that temperature reactions up to 102 F (rectally) have been reduced while the more severe reactions remain about the same (table 5).

Catheter drainage has remained at 2 days postoperatively, with an occasional case being drained for 3 days.

A trend toward shorter postoperative hospitalization continues. The already low average postoperative hospitalization 12 years ago of 10½ days has now been reduced to 8½ days.

Except in those cases where alkaline incrustations have been present and where their recurrence is feared, patients are not sent home on sulfa drug. An adequate resection with good "funnelization" insures a minimum of infection and also an absence of fever or constitutional symptoms. Annoying dysuria during the postoperative and post-hospitalization period is controlled with small doses of methylene blue.

TABLE 5.—*Postoperative temperatures*

	SERIES 1	SERIES 2
Highest postoperative temperature (rectal):		
98.6–100	44	50
100 –101	34	16
101 –102	22	14
102 –103	7	10
103 –104	8	5
104 –105	5	4
105 –106	2	1

POSTOPERATIVE COMPLICATIONS

Hemorrhage, both of the immediate and of the delayed varieties, continues to be an occasionally troublesome complication of the transurethral resection (table 6). Immediate hemorrhage is most often noted on the afternoon of the operative day. While formerly about 3 per cent of these cases had to be returned to the operating room for evaculation of clots and fulguration of bleeding points, we almost never see bleeding of this severity now. We believe that this is due to a more adequate resection together with meticulous control of bleeding before closing the operative procedure. We do not believe continuous irrigation to be necessary or desirable; the vast majority of our resections are never irrigated. Further, transfusion of blood is seldom required unless the patient was previously anemic.

However, it would appear that the number of patients returning in 15 to 25 days postoperatively with a bladder full of clots has not been decreased but remains at from 4 to 6 per cent. This type of secondary hemorrhage has been thought to be due to sloughing tissue which was inadequately resected. That this is not the entire answer is indicated by the fact that we now leave less avascularized tissue than ever before.

During the past year we have discontinued the routine bilateral vasectomy formerly practiced. It has been our impression that the incidence of epididymitis is unchanged whether vasectomy is performed or not. However, comparison of our two groups indicates that 12 years ago 2 per cent of patients developed this complication, whereas today about 5 per cent of patients develop it. This latter figure is close to that reported by Lynn and Nesbit for 300 consecutive transurethral resections done without vasectomy.

The complications of peri-urethral abscess, phlebitis, and incontinence were avoided in the recent series whereas 12 years ago 3 per cent of the cases developed one of these. However, 1 case of bladder neck perforation and 1 case of pulmonary embolus occurred in the recent series while none were recorded 12 years ago. Fortunately, neither of these patients died.

TABLE 6.—*Complications*

	SERIES 1	SERIES 2
I. Hemorrhage		
A. Immediate	8 cases	8 cases
Requiring re-operation	3 cases	0 cases
Requiring irrigating catheter	5 cases	8 cases
B. Delayed	4 cases	6 cases
Requiring anesthesia and re-operation	2 cases	4 cases
Requiring catheter drainage	2 cases	2 cases
II. Epididymitis	2 cases (vas tie)	5 cases (no vas tie)
III. Perforation of bladder (extravasation of urine)	0 cases	1 case
IV. Periurethral abscess	1 case	0 cases
V. Phlebitis	1 case	0 cases
VI. Embolus	0 cases	1 case
VII. Incontinence	1 case	0 cases
VIII. Prolonged frequency and urgency	8 cases	5 cases
Relieved after 60 days	4 cases	1 case
Unrelieved of frequency (carcinoma)	4 cases	4 cases
IX. Inability to empty bladder	6 cases	13 cases
Diverticula	4 cases	4 cases
Atony	1 case	9 cases
Insufficient tissue removal	1 case	0 cases
X. Stricture following operation	3 cases	1 case
XI. Pyuria continuous after 3 months	18 cases	6 cases
Diverticula	7 cases	2 cases
Chronic pyelonephritis	1 case	1 case
Carcinoma with recurring obstruction	6 cases	3 cases
Atony of bladder	2 cases	0 cases
Cystitis (unrelieved)	2 cases	0 cases

One postoperative stricture was encountered in the current series as against 3 cases previously. We believe the reduction in stricture formation to be due to an increased appreciation of the limit to which the urethra can be stretched without forming a stricture. We freely use meatotomy and occasionally a perineal urethrotomy.

PATHOLOGY

Twelve years ago the average amount of tissue removed was 13.72 gm. (table 7). Now the average weight is 30.95 gm. It is interesting that we now routinely remove an average weight of tissue which equals the average reported from a large series of suprapubic prostatectomies. Also, 41 per cent of our resections are in the class which Creevy has designated "the large prostate"; that is, those over 30 gm.

Study of the statistics for the pathological diagnosis of the two series suggests that the viewpoint of the pathologists rather than the distribution of the disease processes has changed. Apparently tissue which 12 years ago we called grade 1 carcinoma, today, with more experience, we would label as benign or as grade 2 or grade 3 carcinomas. In other words, our division of "grade 1 carcinoma" was too broad. In both series somewhere around 75 per cent of cases were benign and around 25 per cent were malignant. It is of passing interest that 2 of our recent patients had leukemia. One case showed leukemic infiltration in the prostatic tissue while the other did not.

TABLE 7.-*Pathology*

	SERIES 1	SERIES 2
Average weight of tissue removed	13.72 gm.	30.95 gm.
gm	*cases*	*cases*
100–150	0	1
90–100	0	2
80– 90	0	1
70– 80	1	3
60– 70	0	9
50– 60	1	2
40– 50	3	11
30– 40	6	12
20– 30	10	12
10– 20	38	30
0– 10	41	17
Benign hypertrophy	74	77
Malignant	26	23
Grade I	17	1
Grade II	6	5 (Leukemia 1)
Grade III	3	16
Grade IV	0	0

RESULTS

An insufficient amount of time has elapsed to completely evaluate our recent series. Since the more complete resection should show its superiority in a decrease in the number of resections for recurrent adenomata, the full evaluation of the second series cannot be made now. The situation today is summarized in table 8.

It is to be noted that on a short term basis the change from 12 years ago is not so great as one might guess. Some 81 per cent of patients now obtain excellent results as against 74 per cent previously. The percentage of patients obtaining good results has decreased from 17 per cent to 12 per cent; this change has been reflected in the increase in the percentage of patients obtaining an excellent result. The percentage of patients with fair results remains unchanged at 6 per cent. While the percentage of poor results fell to none in the recent series, it was only 1 per cent in the 12 year old series.

The mortality rates for both series are shown in table 8 as well as a summary of the 1 death in the recent series. Included in the recent series are 3 patients who have died at home of various causes (heart disease, 2 cases; mental deterioration and cachexia, 1 case). These cases are classified as to their prostatic conditions shortly before death.

TABLE 8.—*Results and mortality*

RESULTS	SERIES 1	SERIES 2
	per cent	*per cent*
Excellent, grade 1 Free, easy, painless urinary stream. No residual. Nocturia 1–2 times. Infection absent.	74	81
Good, grade 2 Free, easy, painless stream. No residual. Nocturia 2–4 times. Infection or pyuria usually present.	17	12
Fair, grade 3 Residual 1 to 4 ounces. Infected. Good control. Nocturia 4–6 times.	6	6
Poor, grade 4 Incontinent.	1	0
MORTALITY	2	1 *Death*—Case 0.0. Age 80. Disoriented, hemiparesis. Blood pressure 210/140. 60 gm. resected. Died of sepsis and broncho-pneumonia—3 days.

SUMMARY

It would seem that the changes and improvements in the transurethral resection during the past 12 years have not been so great as one might at first imagine. We believe that definite improvement in all phases has been made but this has not been so great as that seen in some other surgical fields. A general trend for resecting younger men with less complicated cases together with a more complete resection and a shorter hospitalization period can be noted. Febrile reactions and the majority of complications are slightly less frequent now but such complications as late secondary hemorrhage, epididymitis, and atony of the bladder continue to be troublesome problems. The ratio of benign to malignant glands continues about the same through the years. While we are now resecting a greatly increased average weight of tissue, the results on a short term basis are not strikingly improved. It may, however, be that as fewer patients return with benign recurrences over a period of years the actual superiority of our present day operation will more dramatically be shown.

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TRANSIENT BACTEREMIA IMMEDIATELY FOLLOWING TRANSURETHRAL PROSTATIC RESECTION

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Bacteremia following surgical procedures usually is considered to be transient and harmless. At times, however, bacteremia may initiate septicemia and contribute to postoperative morbidity. Accordingly, we have undertaken a study to evaluate the frequency and significance of bacteremia following transurethral prostatic resection.

Bacteremia during and after operative procedures has been reported in several surgical fields. For example, dental surgeons have cited positive blood culture that followed the extraction and manipulation of teeth or that followed even mastication in persons who had severe gingival disease. Similarly, otolaryngologists have noted bacteria in the blood stream after tonsillectomy. To be more specific, in urologic surgery, Barrington and Wright obtained positive blood cultures immediately after 13 of 23 urethral procedures employed for the treatment of urethral strictures. Similarly, Powers found transient bacteremia in 3 out of 30 cases after urethral instrumentation in the presence of urinary infection.

PROCEDURE

For our investigation, we obtained blood cultures on 106 unselected patients on whom a prostatic transurethral resection was performed during the years 1947 and 1948 at the Mayo Clinic. In 98 of the 106 prostates the disease was benign; in the remainder it was malignant. In every case a blood specimen was drawn immediately at the end of the operation. In addition, in the majority of the cases, a preoperative and a postoperative blood specimen was drawn. The latter was usually collected approximately three or four hours after operation. Whenever practicable, a specimen of urine for culture was obtained at the time the resectoscope was introduced prior to resection.

The method employed for obtaining the blood specimens was identical with that used for routine cultures. Specifically, 15 cc of venous blood was withdrawn from the patient; 10 cc was then placed in a tube of sterile citrate solution and the remainder inoculated into a culture tube containing brain broth. Later, the citrated blood was used for making three poured plates with 0.5, 1 and 3 cc of blood respectively. A plate showing only an occasional surface colony of Micrococcus was not considered representative of a positive culture.

In addition to the bacteriologic investigation, we studied the postoperative course of the patients comprising this series. By so doing, we hoped to evaluate the clinical significance of bacteremia occurring immediately after transurethral resection.

RESULTS

Of the blood cultures obtained from 106 patients immediately at the end of the operation (hereinafter referred to as the operative specimen), 93 were negative and 13 were positive. A preoperative culture was obtained prior to resection in 70 cases; these were all negative. Postoperative blood cultures were obtained three to four hours after operation in 90 cases; all of these were negative except 3.

Table 1. *Results of urine and blood cultures in 13 cases in which bacteremia immediately followed transurethral prostatic resection (106 patients)*

CASE	PREOPERATIVE CULTURE		OPERATIVE BLOOD CULTURE	POSTOPERATIVE BLOOD CULTURE	
	Urine	Blood		After 3 to 4 hours	After 2 or more days
1	Paracolobactrum	Negative	Paracolobactrum	Paracolobactrum	Negative
2	Micrococcus pyogenes	Negative	Micrococcus pyogenes	Negative	
3	Pseudomonas	Not done	Micrococcus pyogenes. Pseudomonas	Micrococcus pyogenes	Negative
4	Micrococcus*	Not done	Micrococcus.* Anaerobic streptococcus	Not done	
5	Not done	Not done	Streptococcus faecalis	Negative	
6	Not done	Negative	Aerobacter aerogenes	Negative	
7	Negative	Not done	Pseudomonas	Not done	
8	Micrococcus*	Not done	Micrococcus*	Negative	
9	Micrococcus*	Not done	Micrococcus*	Micrococcus*	Negative
10	Negative	Negative	Micrococcus*	Negative	
11	Pseudomonas. Streptococcus faecalis. Micrococcus pyogenes	Not done	Escherichia coli	Not done	
12	Negative	Not done	Escherichia coli	Negative	
13	Not done	Not done	Escherichia coli	Negative	

* Species undetermined.

Data on the organisms cultured from the blood specimen withdrawn from the patient immediately at the end of operation are given in table 1. This reveals that pure cultures were obtained in 11 instances and mixed cultures in 2. Escherichia coli and Micrococcus (species undetermined) were found most commonly. The remainder included Micrococcus pyogenes, Pseudomonas, Aerobacter aerogenes, Streptococcus and Paracolobactrum (species undetermined).

Postoperative blood cultures were obtained in 10 of the 13 cases in which positive operative cultures were obtained (table 1). These were collected at an interval of approximately 3 to 4 hours after operation. Seven of these 10 cultures were negative. In 3 the kind of organisms that were found had also been found in the blood specimens withdrawn immediately at the end of the operation from the same patients. Subsequent blood cultures obtained several days later from these 3 patients were negative.

Specimens of urine for culture were obtained through the resectoscope just prior to resection in 10 of the 13 cases in which bacteremia developed (table 1). In 3 of these cases the cultures were negative, in 6 the kind of organisms found in the urine was found also in the blood, and in 1 instance the kind of organisms found in the urine was different from that found in the blood stream.

Our investigation of the possible clinical significance of bacteremia which occurs during transurethral prostatic resection was limited to the study of the postoperative febrile reaction and the postoperative hospital morbidity in this series of 106 cases. We considered only the postoperative fever that occurred between the time of operation and the time of removal of the urethral catheter. Of the 13 patients with positive operative blood cultures, 5 had a temperature that was more than 101 F on the first and second postoperative days; on the other hand, of the 93 patients with negative operative cultures, 23 had a temperature that was more than 101 F. Chills accompanied fever in 3 of the latter group.

The patients in the group with positive operative blood cultures remained in the hospital for periods ranging from 5 to 20 days, the average being 10.8 days, after operation. The postoperative hospital morbidity of those with negative blood cultures ranged from 4 to 34 days, with an average of 7.9 days. These results appear to show that the average hospital morbidity for the group of patients having positive operative blood cultures was 2.9 days longer than those with negative operative cultures.

COMMENT

Any bacteriologic study is subject to the criticism that some of the so-called positive cultures may actually represent contaminants. Our results, however, appear to show that we confined such contamination to a minimum. One indication of this is that all 70 of the preoperative cultures obtained by standard technique were negative without exception. Another indication is the data concerning the cultures obtained from the patients three to four hours after operation. Of 90 such cultures, 87 were negative while in 3 the kind of organisms cultured had been found also in the same patient at the time of operation three or four hours previously. If the organisms grown from the specimens collected at the time of operation were contaminants, one would hardly expect to culture the same contaminants in subsequent cultures from the same patients. Furthermore, while some of the organisms cultured in this group might possibly be contaminants, all of them are known inhabitants of the urine and prostate. Therefore, the supposition that the source of these bacteria was the urinary tract seems reasonable.

Since we have been unable to find a report of any similar study in the literature, we are unable to compare our incidence of 13 positive operative cultures in 106 cases with that of other investigators. However, various dental surgeons have reported an incidence of transient bacteremia after tooth extraction, of 16.9 to 83.3 per cent. Interestingly enough, transitory bacteremia has been found in 20 to 56 per cent of patients both after mastication and after merely rocking the teeth. Similarly, positive blood cultures have been reported in as high as 38 per cent of patients after tonsillectomy. We have already cited the work of Barrington and Wright who found 13 positive blood cultures when specimens were obtained immediately after procedures employed for treatment of urethral stricture in 23 patients. Powers also obtained blood cultures immediately after urethral instrumentation of 30 patients who were known to have infection of the urinary tract. Three of these patients had transient bacteremia.

The kinds of organisms grown in this series of positive cultures are either found in the urine or have been cultured from prostatic tissue. Bacilli of the colon group and cocci classified as Micrococcus (species undetermined) were the most common organisms cultured. Other bacteria included Micrococcus pyogenes, Streptococcus faecalis, Pseudomonas and Streptococcus (anaerobic). The predominance of colon bacilli agrees with the findings of Barrington and Wright who found Escherichia coli to be the most common bacteria encountered in the blood stream of their urologic patients. Similarly, Powers reported that Escherichia coli was the organism in 2 of the 3 positive blood cultures he obtained from patients immediately after urethral manipulation. By contrast, the organism cultured most commonly from the blood stream after dental operations has been Streptococcus viridans, while various species of Streptococcus and Staphylococcus have been grown in blood cultures obtained after tonsillectomy.

The fact that of 7 positive urine cultures obtained preoperatively in our group of patients with bacteremia, 6 were positive for the same organisms as were grown in the operative blood specimen secured from the same patients may indicate that the source of bacteremia in these particular cases was the urine.

We made no attempt to estimate how long the bacteremia persisted in our cases. In 3 instances, however, blood cultures taken as long as 3 or 4 hours postoperatively were positive. Subsequent cultures taken two to several days after operation in these 3 cases were negative. Others have demonstrated experimentally that such bacteremia is usually very transient in animals. Supposedly, the bacteria are removed from the blood stream by the reticulo-endothelial system.

The mode of entrance of these bacteria into the blood stream has not been proved. However, the work of Creevy and Webb and Creevy, which has since been confirmed by other investigators, furnishes a logical explanation for the transfer of bacteria from the urologic tract to the blood stream during transurethral resection. Creevy and Webb were the first to demonstrate hemoglobinemia during resection. They concluded that such hemolysis was caused by the sterile water used as an irrigating fluid which had been forced into the blood stream via the prostatic sinuses opened during the resection. Landsteiner and Finch gave credence to this theory when, after "labeling" irrigating fluid employed in one of their resections, they calculated that approximately a quart of the fluid had entered the patient's circulation. Therefore, the supposition that

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LEIOMYOSARCOMA OF PROSTATE

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Mr. C. P., aged 53, came to the office complaining of perineal pain, nocturia, and dysuria of 6 weeks' duration. The pain was aggravated by bowel movements. Examination was essentially negative except for a markedly enlarged, soft prostate. Only a minimal amount of periprostatic induration could be palpated. An abscess was diagnosed and penicillin treatment initiated. After 7 days' treatment there was no improvement and the patient was hospitalized on February 23, 1947.

At admission there were no additional significant physical findings. The blood count and urine examinations were normal. The blood urea showed 13.4 mg. per 100 cc. The blood phosphatase showed 5.63 u. The chest x-ray was negative.

Cystoscopy on February 24 showed enormous lateral prostatic lobes which occluded the retromontane urethra. There was no evidence of infection. Both lateral lobes were deeply incised with the cutting loop. There was no pus. The tissue was pale gray, homogeneous and soft. The microscopic sections showed a leiomyosarcoma of the prostate. Proctoscopic examination revealed no rectal involvement. Deep x-ray therapy consisting of 5,500 r. was immediately given without clinical improvement.

On March 10, 1947, a bilateral subcapsular orchiectomy was carried out, endeavoring to control tumor growth. On March 19, 1947 abdominal exploration revealed extension of the prostatic tumor into the base of the urinary bladder, parietal peritoneum and pouch of Douglas. The left pelvic ureter was dilated. The findings precluded ureteral transplantation and cystectomy. On April 16, 30 gm. of prostatic tumor tissue were removed transurethrally for urinary retention. The patient failed rapidly and expired on May 18, 1947.

At autopsy, the unusual anatomic changes were in the pelvis. Focal acute fibropurulent exudate was present around the bladder dome and the adjacent loops of small intestine. White nodules of tumor tissue laid on the peritoneum of the anterior abdominal wall and of the pelvis. In the base of the urinary bladder there was a large fungating, soft, partially necrotic, pale gray polypoid mass which extended from the prostate. Dissection was impaired by the diffuse tumor invasion. The openings of the ureters were obstructed by the new growth. One metastasis was seen in the upper pole of the left kidney. Slight hydroureter and hydronephrosis were present bilaterally.

Sections of the neoplasm showed normal prostate in various regions merging with abnormal tissue. This consisted of elongated, fusiform cells arranged in no pattern and lying intermingled with themselves. The nuclear cytoplasmic ratio was increased. Bizarre nuclear forms and tumor giant cells were common. Vascular slits were frequent. No true blood vessel invasion was seen. Extension into the urinary bladder was readily demonstrated. By special stains the cells were shown to be muscle. No striations or "bearded" nuclei were seen.

The autopsy confirmed the diagnosis made on the excised tissue of leiomyosarcoma arising in the prostate. This had invaded the rectum and urinary bladder.

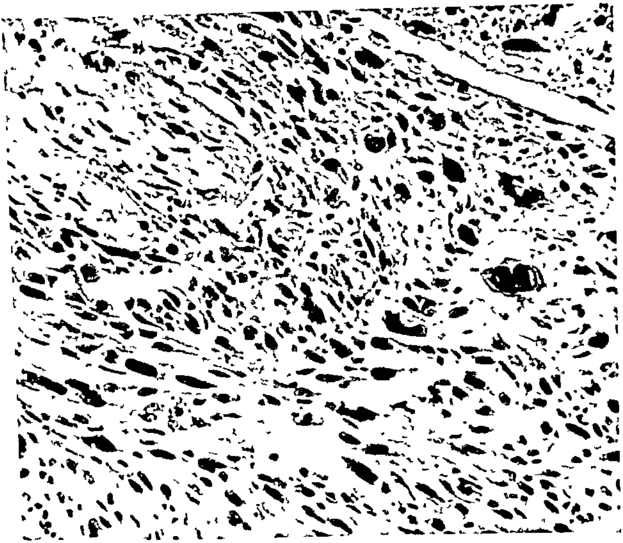

FIG 1 Sarcoma of muscle with tumor giant cells Formalin fixation, hematoxylin and eosin stain × 100

DISCUSSION

In 1939, Stirling and Ash, and in 1943, Melicow, Pelton and Fish presented concise and rather complete reviews on the subject of sarcoma of the prostate.

Some 200 cases of this neoplasm had been reported up until 1943, the first by Stafford of London in 1838 (without histologic study) and the first proved microscopically by Isambert in 1853.

It occurs once in 1000 prostatic neoplasms, both non-malignant and malignant.

Symptoms are those of vesical neck obstruction with an insidious painless onset. The rapidly expanding new growth presses upon adjacent tissues and organs with the associated secondary signs.

Treatment is surgical and radiation in combination. The results are poor and fatality occurs within months. There is a marked selection for younger males.

Positive diagnosis is established by morphologic study.

Various types are included dependent upon the tissue of origin; fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, myxosarcoma and lymphosarcoma. There is slight variation in the course as a result of the histologic type.

SUMMARY

A case of leiomyosarcoma of the prostate is presented with a brief discussion of the salient features.

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THE IVANISSEVITCH OPERATION

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For many years varicoceles have been treated by one of several methods, namely, operation by way of the scrotum with ligation of the veins en masse, injection, and suspension with a suspensory The results of these methods have never been entirely satisfactory When the anatomy of the internal spermatic vein is considered, it becomes obvious that if this vein could be ligated above the pampiniform plexus, the varicosities would be eliminated (This is consistent with the treatment of varicosities elsewhere) This procedure has been suggested and tried by several urologists in recent years and it was their good results on a few patients that prompted this work on a large series of patients One need not worry about the venous return from the testicle since it is taken over by collaterals to the pudendal system

In a survey of over 1500 young men of army age (table 1) it was found that 16 5 per cent had varicocoeles These were classified according to size into three classes The first class is those that are large, with the left testicle considerably lower than the right These men all complained of symptoms such as pain, dragging sensation, and noticeable testicular atrophy Most of them wore a suspensory of some sort This class comprised the small asymptomatic varicoceles The testicle usually did not hang any lower than normal and often the man had given no thought to its presence This class comprised 55 per cent of the total or 9 per cent of all men examined

The third class consisted of those who were in between the other two in size and were symptomatic Thus some of class 2 in size were placed in this class because of symptoms This class comprised 30 per cent of the total or 5 per cent of all examined Only 1 per cent of those with varicocele on the left side had varicocele on the right also and there were no cases of varicocele on the right side only

These cases represent a consecutive period on series consisting of 42 patients (table 2) The patients were all of the white race The incidence in Negroes has been stated to be around 1 per cent

TECHNIQUE

Spinal anesthesia, 12 mg pontocaine in 1 5 cc spinal fluid, has been used in all cases A 2 inch incision is made parallel to and just above Poupart's ligament The fascia of the external oblique is divided in the line of its fibers The cord is dissected free by blunt dissection and lifted from its bed The infundibuliform and cremasteric fascias are opened and the cord examined for a sac of peritoneum This sac was found in 8 cases When a hernia sac is found, the wound is elongated and the fascia split further to give more exposure The sac is dissected free, opened and ligated with catgut A typical hernia repair of the external oblique fascia is then done The spermatic vein is isolated, divided, and ligated In most cases more than one vein was found It is absolutely necessary to find and ligate all branches of the spermatic vein to prevent recurrence. Care must be taken to prevent injury to the vas and artery. In 5 cases the varicocele was so large and the testicle hung so low that it was believed that suspension of the testicle was necessary. This is accomplished by delivering the testicle with its tunics into the wound, doing a bottle type hydrocelectomy, and using the tunica to suspend the testicle. Cotton thread has been used throughout. Postoperative care consists of suspensory and ice bag for 24 hours. The patient is made to get up the day after surgery and is usually discharged from the hospital on the seventh to ninth day. Several of the simple ligations were able to resume light duty on the fifth postoperative day.

TABLE 1

	%	% TOTAL
Class I		
severe	15	2.5
Class II		
small asymptomatic	55	9
Class III		
moderate or small symptomatic	30	5
	100	16.5

TABLE 2

Simple ligation	27
Ligation both sides	2
Ligation and suspension	5
Ligation and herniorrhaphy	8
Total	42

The results of this treatment, as determined by a follow-up of 1 to 2 years, have been very satisfactory. It was necessary to repeat the operation on 2 patients because of veins missed during the first procedure. This emphasizes the necessity of ligating all branches of the spermatic vein. Another patient has written that his varicocele is larger than before surgery. He hasn't been examined but it is likely that another ligation will be necessary. One patient, who had to be talked into surgery, wrote 4 months later that he had been skiing and mountain climbing and that he never realized how much the varicocele had bothered him until it was cured.

There have been no complications noted as yet from this operation. In the other methods, hydroceles, hematoceles and atrophy of the testicle have been noted. By going in above Poupart's ligament the first two are prevented. Also the skin preparation is much easier and better above Poupart's ligament than via the scrotum. For this reason there have been no cases of abscess or infection. No increase in testicular atrophy has been noted, and there has been no atrophy where there was none before surgery In no case has there been late postoperative pain

SUMMARY

Emphasis is placed on a new method of treating varicoceles by high ligation of the internal spermatic vein The incidence of varicoceles is given as found in young healthy men It is recommended that this new method be used as it is easily modified to cope with all possibilities

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PERMANENT ARTIFICIAL (SILICONE) URETHRA

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The case reported below is presented for two reasons: 1) for the unusual history of prolonged urethral mutilation resulting in a totally destroyed posterior urethra; and 2) this is the first report in the literature of apparently successful replacement of the human male urethra by artificial means.

CASE REPORT

G. D., a 49 year old Negro, was admitted to the Kadlec Hospital April 14, 1948, for the relief of urinary retention. His good health was interrupted 30 years before admission by acute urethritis, presumably gonococcal in origin. There was no treatment, and symptoms subsided in 2 weeks. Approximately 3 years later difficulty in urination first occurred and for the next 10 years treatment consisted of urethral dilatation, "sometimes by doctors and sometimes by friends and others who knew how to break the stricture." At the age of 28 urination consisted only of prolonged dribbling after great strain and an internal "boring out" was done by a colored "doctor" who often treated the Negroes in the patient's neighborhood, but was known not to be a licensed physician. The night of this "operation" the urine had all gone into the scrotal "sacs" (the patient describing the symptoms of extravasation of urine). Bed rest for 11 days brought little improvement and the patient entered an unremembered hospital where the first suprapubic cystotomy was done, supplemented by numerous scrotal incisions. Following discharge from the hospital, urination was little improved and urethral sounding was frequently done, sometimes by the patient himself using a blunted screw driver.

For the next 12 years the history is even less specific as little can be remembered, except that continued urethral mutilation occurred. The patient states that during this period he "like as not was drunk most of the time." However, although the time and place are not recalled, a second suprapubic cystotomy was done during this period and the patient was advised not to remove the tube from his abdomen which he later did. During this period he also was treated for "spinal syphilis" for a "few weeks."

Approximately 1 year following the second suprapubic cystotomy, the operation was repeated for the third time and a short while following removal of the suprapubic catheter an opening occurred in the right scrotal sac from which urine continually dribbled. The patient states that by this time his penis and scrotal sacs were enlarged to four or five times the normal size and he was in almost constant pain. Complete retention occurred often, but he would "just wait it out" or "stick something in one of the holes" and relief would follow a gush or dribble of urine.

During the 8 years preceding admission to the Kadlec hospital, two other urethral fistulas occurred, so that urine would dribble from either the glans penis, a urethroscrotal fistula, or the right or left urethro-perineal fistulas. Often large abscesses occurred in these areas which would eventually discharge pus and urine.

During the 2 weeks preceding admission, there had been slight urinary discharge from all fistulas. Urethral voiding had not occurred at all, huge painful swellings had developed in both groins and during the past 48 hours all fistulas had closed. The patient, therefore, presented himself in severe pain and extensive urinary retention.

The temperature was 100.6 F, pulse 90, respiration 20, blood pressure 120/70. The significant findings were disclosed on examination of the abdomen and genital organs. There was moderate obesity of the upper and lateral regions of the abdomen, but from the umbilicus to the pubis, the abdomen was markedly indented and drawn together in a 10 cm. by 6 cm. area of thick board-like scar. Over the pubis and base of the penis a diffuse, soft, adipose-like swelling was felt which was in sharp contrast to markedly swollen, tender and indurated areas in both groins, each of which drained a small amount of thin yellow pus. There was moderate elephantiasis of the penis and left scrotum. The right scrotum was shrunken in which scar tissue and neither testicle was felt. Fistulas were found in the left scrotal area and in the right and left perineal regions. These were superficially probed, but no drainage occurred.

The hemoglobin was 12.5; red blood count 4,320,000; white blood count, 9,800. The blood urea taken 2 and 8 days following operation was 19 mg. The blood Kahn was negative. Frei antigen test was negative at 24, 48 and 72 hours. Culture of the scrotal and groin pus revealed Escherichia coli.

Attempts to sound and catheterize the patient under local anesthesia were unsuccessful, but were followed by a small amount of urinary flow from the urethra. Warm saline packs to the groin caused the rupture of the right groin abscess with some urinary drainage, but in 24 hours it was apparent that a fourth suprapubic cystostomy was indicated. Accordingly a routine suprapubic cystotomy was done under sodium pentothal anesthesia supplemented with curare. Difficulty was encounteed in finding and freeing the urinary bladder which was trapped in scar tissue. However, the peritoneum was not opened and when finally liberated the bladder was found to be normal except for distention with 1200 cc of murky brownish urine. A large mushroom catheter was placed in the bladder and the surrounding tissues extensively drained. The tumors in the groin consisted of indurated "sarcomatous-like" tissue. A biopsy was taken and multiple incisions were made in these areas for drainage. The wound was loosely closed with No. 0 chromic catgut and warm saline packs were applied to the lower abdomen.

The postoperative course was singularly uneventful. The temperature remained low-grade. The patient appeared comfortable, ate a regular diet and intake and output were at all times adequate. Chemotherapy consisted of 75,000 units of penicillin and 300 mg. of streptomycin every 3 hours. Sulfanilamide in regular doses was added following receipt of the report on the biopsied tissue which read "sub-acute inflammation with abscess formation (? chancroid)."

Two weeks following the operation the suprapubic and groin wounds had healed. The suprapubic catheter was draining well, but all three urethral fistulas were intermittantly draining small amounts of urine. The patient was up and about and more definitive and permanent therapy in the form of urethral reconstruction was indicated.

On May 5, 1948 a second operation was done under the same general anesthesia. The patient was placed and draped in the lithotomy position, the operator thereby having access to both the abdomen and perineal regions. A No. 16 sound was placed in the pendulous urethra but was blocked within 4 inches of the glans penis. Accordingly a finger was placed in the suprapubic wound, the mushroom catheter was removed and suprapubic and bladder wounds were enlarged. With one finger in the internal opening of the urethra (through the bladder) the elephantitic penis and scrotum were held up and a transverse perineal incision was made to the central tendinous point of the perineum in the region of the posterior and prostatic urethra. A small sound was externally placed in the penile urethra and by pushing and teasing the instrument was made to emerge through thick scar tissue into the perineal opening. There was no evidence in this area of any structure resembling urethra. Another small sound was placed into the remnants of the posterior urethra from within the bladder and by similar pushing was also made to emerge through the perineal wound. A block dissection of scar tissue in this region was then performed. Care was taken to avoid the region of the external sphincter. A small catheter was placed over the tip of the sound traversing the bladder and remnant (not apparent) of the posterior urethra and this catheter was drawn into the bladder. The catheter was then threaded through a $3\frac{3}{4}$ inch silicon tube (General Electric Co.) (fig. 1). The objective was to use the silicon tube as a permanent complete posterior urethra and partial pendulous urethra. The distal end of the catheter was then brought out the remaining pendulous urethra over the sound which had been placed through it (fig. 2). The silicon tube was then lightly tied over the ridge on its middle to the surrounding scar tissue at the base of the penis with a medium silk suture ligature.

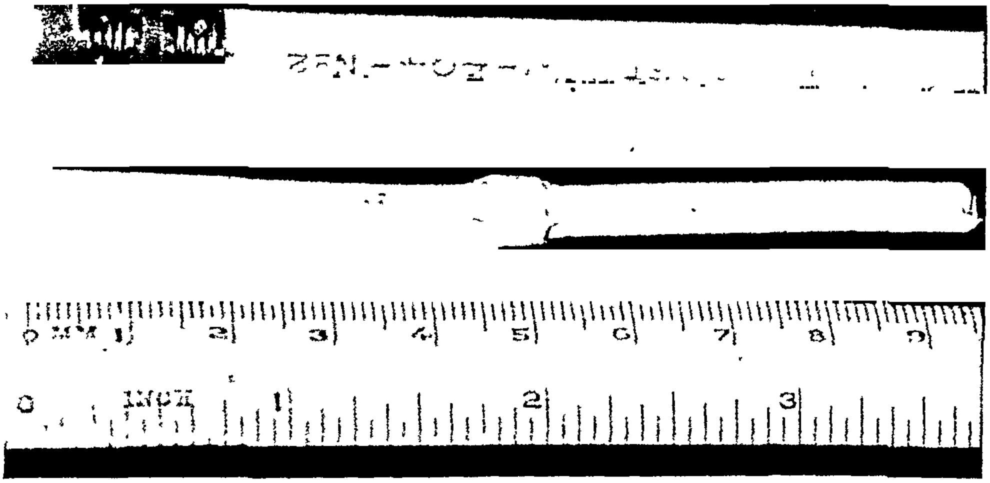

FIG. 1. Silicon tube used to replace destroyed urethra

The flexible silicon tube was then adjusted to the contour at the base of the penis and care was exercised not to encroach on the external sphincter to allow for voluntary urinary control. The perineal and suprapubic wounds were lightly closed with interrupted medium silk sutures. The suprapubic mushroom catheter was replaced in the bladder and both the abdominal and perineal wounds were drained by Penrose tubes.

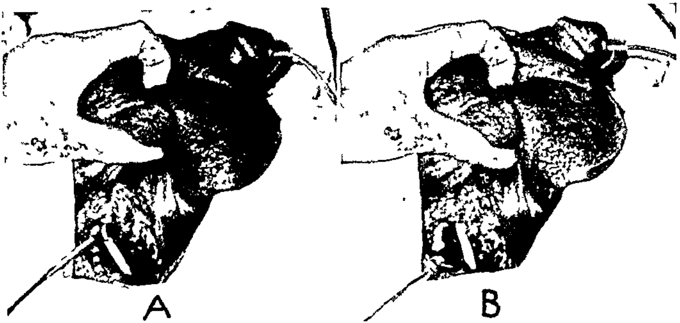

FIG. 2. *A*, artificial urethra shown with a small catheter threaded through it. *B*, silicon tube shown snug in its permanent position Following this, perineal wound was closed. A catheter draining bladder traverses tube, and is seen emerging from penile urethra.

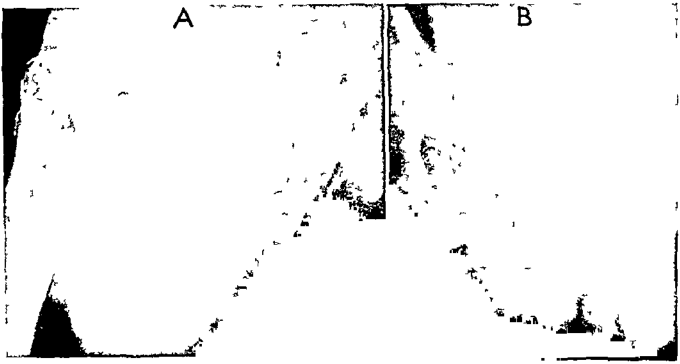

FIG. 3. *A*, x-ray retouched for clarity. Contour of [illegible]. Penis and scrotum are seen in outline *B*, antero-posterior view [illegible] its relation to pubis, penis and scrotum. Normal curve of posterior urethra is apparent.

The postoperative course was again uneventful. The same chemotherapy was ordered for 5 days. All drains were removed by the fifth postoperative day. Clear urine drained from both the urethral and bladder catheters and the wounds healed cleanly. The urethral fistulas ceased to drain and closed permanently by the tenth postoperative day. The suprapubic catheter was removed after 2 weeks and the abdominal wound closed within 4 days. The patient was up and about

17 days after the operation and the urethral catheter was clamped off (following completed healing of the suprapubic wound) and opened every 3 hours at which time the patient was instructed to attempt to void through the catheter. A stream of urine under moderate pressure indicated some voluntary control. He was discharged 21 days following the second operation with the urethral catheter still threaded through the silicon tube and instructed to continue the three hour draining program.

Five weeks following operation, the catheter was removed in the surgical clinic. Fortunately the silicon tube had formed no adherance to it and remained in position. Several minutes later the patient voided 258 cc of urine spontaneously. It was apparent that he had "stop and go" control and he remarked that he had not voided in such a manner in at least 15 years. The artificial urethra has now functioned almost normally for nearly 5 months. The perineal wound showed a pin point opening for a short time and leaked an occasional drop of urine. This opening closed after several applications of silver nitrate. The urethral fistulas have remained closed and all wounds are healed. X-rays of the pelvis show how the flexible tube has remained in position and follows the normal contour of the posterior urethra and penis (fig. 3). There has been no sexual impotency.

Addendum: At the end of 14 months the artificial urethra had been retained with normal genito-urinary function. Urinary symptoms of infection on two occasions quickly subsided under sulfathiazole treatment.

COMMENT

It is impossible to use the word "permanent" in connection with this prosthesis. However there is no evidence at this time that the tube is acting as a foreign body irritant, nor is there evidence of stiffening or plugging. It is quite possible that the urethral mucosa has been replaced, the silicon tube acting as a splint. In view of the extensive destruction and the environment of scar tissue this does not seem probable and an attempt to remove the tube does not seem logical.

The silicon tube used in this patient was originally constructed for use in connection with common bile duct reconstructions. Lahey has used it because of the advantage of flexibility as compared to vitallium tubes. It was mainly the characteristic of flexibility that prompted the use of this tube in this region, and the hope that organic material such as mucus or pus would not adhere to its surface and that liming would not occur. Ferris and Grindlay have shown the extensive amount of liming which occurs even after a few days when ordinary rubber tubes are used as urinary drainage tubes in connection with nephrostomy and ureterostomy procedures. It is possible that the polythene and polyvinyl tubing they have described could be used in the same manner as the silicon tube in urethral reconstructions.

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THE ERYTHROPLASIA OF QUEYRAT TWO CASE REPORTS

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Erythroplasia occurring on the penis was noted by Paget in 1874, Tarnowsky in 1891, and Fournier and Darier in 1893 However, the lesion was so thoroughly studied and described by Queyrat in 1911 that the disease has since been known by his name It had not been encountered or possibly not recognized in this country until Sulzberger and Satenstein called the attention of the profession to it with a case presentation in 1933 Prior to that time the American urological and dermatological literatures contain no reference to this disease Since then about half a score of papers and case reports have appeared on the subject in this country

While the lesion may occur on other structures, namely, the clitoris, vulva, buccal mucosa, and skin, its greatest predeliction is for the glans penis and as such it is of interest to urologists Furthermore, it is generally agreed that it is a precancerous lesion The latter fact doubly emphasizes its importance

Clinically the disease appears as a sharply circumscribed, deeply erythematous, elevated lesion It involves the glans penis most commonly but its proximal margins may also extend on to the prepuce It has a characteristic shiny, velvety appearance Fine scaling and superficial ulceration may occur Marginal leukoplakia is also occasionally seen

It was thought originally that there was some etiological connection between this disease and syphilitic infection However, no constant relation between the two has ever actually been demonstrated and its etiology remains obscure All ages may be affected Its occurrence in Negroes is rare

Histopathologically the lesion is characterized by acanthotic changes, edema in and between the cells of the epidermis, vascular dilatation and marginal infiltration in the dermis If untreated, malignant change very commonly takes place, and early metastases are prone to occur

Dermatologists, who have written most extensively on the subject, are in disagreement as to the proper mode of treatment Some have stated that only very radical therapy is indicated, namely, amputation of the penis On the other hand it has also been suggested that bland ointments, dusting powders, and the avoidance of friction are sufficient The latter group maintain that any other form of local treatment including x-ray and radium predisposes the lesion to malignant change The majority, however, take the view that thorough local electrocoagulation is the most efficacious therapy

We have encountered 2 cases of the erythroplasia of Queyrat during the past 2 years Because the condition is rather unique and probably unfamiliar to many, we feel the cases merit reporting Once encountered the diagnosis is not difficult if the disease is borne in mind

CASE REPORTS

Case 1. J. F., H. F. H. No. 491363, was a 24 year old unmarried white man who was first seen by us in November 1946. The history dated back 6 weeks at which time he noted the appearance of a painless, red lesion on the ventral surface of the glans adjacent to the meatus. Prior to the onset he had had a urethral discharge which responded satisfactorily to several injections of penicillin administered elsewhere. He was first admitted to a near-by rapid treatment center where repeated dark field examinations and blood serological studies were negative. A biopsy was then done. The pathologist reported: "Leukoplakia with epithelial hypertrophy and increased vascularity in the dermis. No malignancy in this material. Histologically compatible with the diagnosis of erythroplasia of Queyrat." When seen by us the lesion was noted to be a sharply circumscribed,

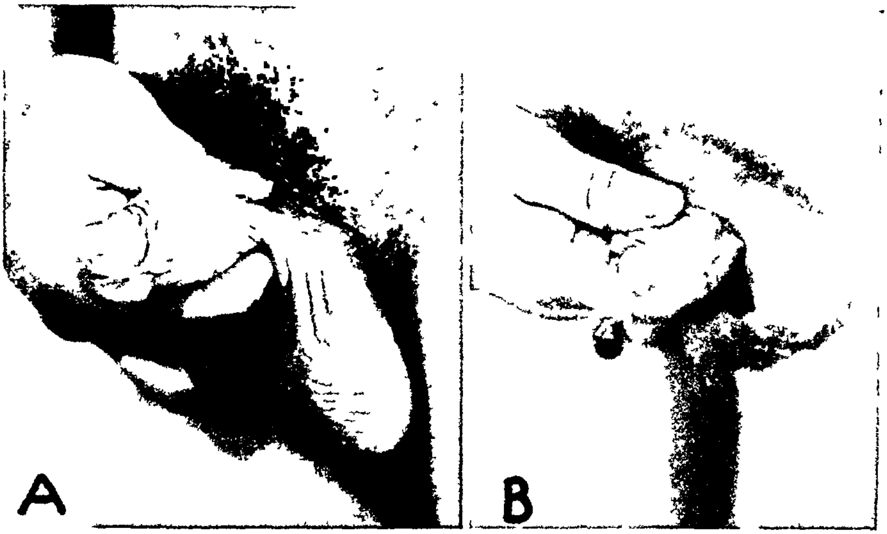

FIG. 1. *A*, showing elevated, sharply marginated lesion on ventral surface of glans. *B*, same region 2 years later.

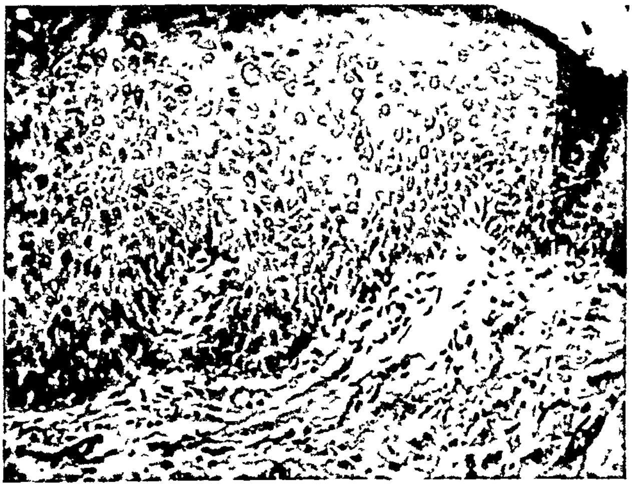

FIG. 2. Photomicrograph of biopsy specimen, showing sharp change from normal epithelium to area of erythroplasia.

non-tender, raised, deeply erythematous, velvety one located on the glans penis near the frenum (fig. 1, *A*).

Under local anesthesia the lesion and immediately adjacent areas were deeply fulgurated. He was followed for a month after operation. The fulgurated area was healing well. He then failed to appear for his follow up examinations. About 2 years later, in October 1948, he visited the clinic again and complained of a morning urethral discharge. The previously fulgurated area had completely healed. There was no sign of a recurrence of the original disease (fig. 1, *B*). The discharge resulted from a chronic non specific prostatitis which responded in a satisfactory manner to the usual therapy. Cysto endoscopic examination disclosed only posterior urethritis.

Case 2. L. Y., H. F. H. No. 43949, was a 70 year old man who was hospitalized because of a cerebrovascular accident. In November 1947 he was noted to have an erythematous lesion on the glans penis. This was originally thought to be a simple non specific balanitis and was so treated but without success. When seen again approximately 9 months later a distinctly different appearing lesion was found. It was now raised, sharply marginated, erythematous, and velvety in appearance. The ventral surface of the glans penis, coronal sulcus, and adjacent prepuce were involved. The proximal edge was faintly leukoplakic, and a fine silvery scale surmounted the lesion. A biopsy was reported as follows: "Microscopically epidermis of normal appearance changes sharply to a thickened atypical epithelium. The retepegs are increased in length and breadth and made up of closely packed cells. The cytoplasm of the cells are sometimes vacuolated and the nuclei are often enlarged and abnormal. A few mitotic figures are evident. The corium contains small collections of inflammatory cells and dilated blood vessels. The findings are compatible with a diagnosis of the erythroplasia of Queyrat" (fig. 2).

Under local anesthesia the involved area of the penis and adjacent tissues were deeply fulgurated. Satisfactory healing took place. Two months after treatment it was complete and no evidence of recurrence was present.

SUMMARY AND CONCLUSIONS

Two cases of the erythroplasia of Queyrat are presented. Both were treated by thorough fulguration with good results. The precancerous nature of the lesion requires familiarity with it so that early diagnosis and treatment will be possible.

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CONGENITAL ABSENCE OF THE VAS DEFERENS: A REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

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An extensive search of the literature was made and little mention of the congenital absence or aplasia of the vas deferens could be found. Although this is one of the most uncommon causes of sterility in the male, it should be taken into consideration. The following reports have been made of this rare condition. Anorchidism, exstrophy of the bladder and hermaphrodism were not included in this series for obvious reasons.

In 1755, John Hunter dissected a cadaver in which the caudal inch of both epididymes was missing. The right vas deferens began in a blunt point in the inguinal canal and ended at the seminal vesicle. The left vas deferens began where the epididymis should have ended and continued to the seminal vesicle of that side. No ejaculatory duct was present on either side.

In 1786, G. Brugnone reported that in dissecting the parts of generation in a robust man 26 or 27 years of age, who died of peripneumonia, he accidentally found the right epididymis almost entirely absent. The only part remaining was the head, which formed a nodule filled with semen. The remainder of the epididymis and vas deferens was absent, without any mark of disease. The testis was sound, and nearly of the same size as the left one.

In 1813, H. Bosscha reported a case of a robust and otherwise well-formed man in whom the whole left vas deferens was wanting except 2 inches that ascends from its natural connection with the epididymis. There was a rudiment of the left vesicula seminalis in the form of a blindly ending canal running tortuously in the shape of the letter S. The left testis was normal.

In 1840, James Paget found at an anatomical dissection on a 71 year old man, who had died of an acute inflammation of the esophagus, that the left vas deferens was not present in the vascular pedicle, which was attached to a mass of an ovoid form (possibly an atrophied testis) in the scrotum. The remains of the vas deferens on this side was found beginning in the inguinal ring and ending normally in the ejaculatory duct and seminal vesicle.

On March 2, 1849, M. Gosselin, while dissecting a cadver of a man of about 20 years old, noted the absence of the right vas deferens between the epididymis and the upper part of the bladder.

In 1870, M. Reverdin, while performing an autopsy, found an absence of the kidney, ureter, vas deferens, and seminal vesicle on the left side, with the existence of two normal testes in the scrotum.

In 1873, T. E. Little summarized his case as follows: "Phenomena of the specimen may be briefly summed up viz.: Absence of the lower part of the epididymis on both sides and of the entire vasa deferentia, with a rudimentary condition of the vesicular seminalis with a normal and healthy condition of all the rest of the generative organs."

In 1905, P. Guizetti found at the autopsy on a 25 year old male, who died of pneumonia, an entire absence of the right vas deferens and vesicle The rest of the urogenital organs was normal

In 1918, V Lespinasse reported 2 cases with absence of both vasa deferentia, one patient with congenital absence and one with acquired (?) absence of the vas, together with an acquired absence of the tail and lower portion of the body of the epididymis The latter patient gave a history that his first wife gave birth to a child who lived only 3 months

In 1927, R T Schwarzwald collected 5 cases of absence of the vas deferens In 2 cases the seminal vesicles were also absent, in 1 case the seminal vesicle was present, and in 2 cases the seminal vesicles were present but only rudimentary

In 1928, Herbert Coe reported a case of a 19 year old male who was physically immature He had the genitalia of a 3 or 4 year old boy and both testes were undescended At operation, the right vas deferens was normal in the inguinal canal but disappeared near the testis in a thread-like band The epididymis and testis were normal but small

In August 1931, A Priesel performed a necropsy on a 47 year old man who died of softening of the brain and arteriosclerotic disease of the kidney He found congenital absence of both vasa deferentia, with normal urinary passages, seminal vesicles and testes

In 1936, Jahfier reported 1 case of absence of the vas deferens

In 1936, Balzar and Weber reported congenital absence of the vasa deferentia at necropsy in two males, aged 77 and 79 respectively In the first there was absence of both vasa deferentia except for a small remnant of the right coming from the seminal vesicle, and the rest of the genitalia was normal The second had a bilateral absence of both vasa deferentia with dilatation and increased tortuosity of both seminal vesicles, the remainder of the genitalia was normal.

In 1937, E Vorstoffel reported absence of the left vas deferens associated with aplasia of the left kidney and hypospadias in a 31 year old male

In 1940, B Dirr reported 1 case of congenital absence of the vas deferens

In 1944, Oleson and Faber reported 2 cases of bilateral aplasia of the vas deferens They showed at biopsy that spermatogenesis of the testes was apparently normal

In 1948, Keshin and Pinck reported 1 case of bilateral absence of the vas deferens with both epididymes showing abnormal configurations but a normal globus major

In reviewing the literature, only 25 cases of absence of the vas deferens were reported I am reporting 3 additional cases of this anomaly—the first 2 cases found by the Lahey Clinic urological service while I was a member of the staff and the last case found during my private practice I will review the embryology of the formation of the duct system of the male genital system before reporting these cases

EMBRYOLOGY OF GENITAL DUCT SYSTEM

The wolffian body or mesonephros is the second urogenital system It takes its origin from an unsegmented mass of mesoderm lying below the tenth primitive segment. The wolffian, or mesonephric duct, takes a downward direction at the same time that the kidney moves upward. While this is taking place, a progressive degeneration of the cranial tubules occurs, with formation of new tubules caudally. This wavelike descent takes 4 months for completion and proceeds until the upper three-fourths of the tubules are lost. The remaining duct is salvaged by the male genital system and is used later in the embryonic development. The tubules, which have escaped degeneration by the tenth week, become divided into a cranial and a caudal group.

The cranial set, now having 5 to 12 tubules, moves downward and at the same time becomes more and more convoluted. About the third month these cranial tubules meet the primordial rete testis and unite with the cordi of the rete testis. The lumen of the tubules become continuous with those of the rete testis and thereby form the efferent ductules of the epididymis by the end of the sixth month. At the same time, the upper end of the cranial portion of the mesonephric or wolffian duct becomes coiled and forms the duct of the epididymis.

The caudal and longest portion of the mesonephric duct forms the vas deferens. The lower end of it meets that of the opposite side behind the bladder and forms the ejaculatory ducts opening into the urogenital sinus. The lowest portion increases greatly in size and forms the ampulla of the vas deferens. Evagination lateralward from this portion of the duct occurs about the thirteenth week. Later it grows laterally and backward, and finally forms the seminal vesicle.

Between the seventh and ninth months the testis moves downward with the help of the gubernaculum. This is a rapid mass movement. At this time the testis and its spermatic cord, consisting of the spermatic vessels and vas deferens, are brought into the scrotum.

CASE REPORTS

Case 1. A 37 year old Italian was seen by the urologic department of the Lahey Clinic because of sterility of either his wife or himself. Although the couple had been married 10 years, and had never used contraceptives, the wife had not become pregnant. The past history was negative other than that the husband had scarlet fever when a child and in 1930 gonorrhea of a very mild type leaving no sequelae.

The patient was of small stature but normally developed and in apparently good health. He weighed 128 pounds and was 5 feet 3 inches tall. The blood pressure was 120 mm. systolic and 84 mm. diastolic; pulse was 70 per minute and regular in rhythm and the oral temperature was 98.6 F. The teeth showed moderate pyorrhea. There was slight atrophy of the right shoulder girdle with some tenderness but no fixation. Examination of the genitalia revealed a small penis and testes of normal size and consistency. The epididymes and prostate were normal and a smear of the latter in the wet state was also normal. The remainder of the physical examination was essentially normal. Urinalysis on January 23, 1945 revealed albumin 1 plus, sugar negative, and a sediment of 2 to 4 leukocytes per high power field. The blood obtained the same day showed the hemoglobin to be 16.3 gm. or 104 per cent, white blood cells 8,450, sedimentation rate 9 mm the first hour, and Hinton negative On February 6, 1945, a semen sample was obtained which revealed no sperm

The patient entered the hospital on May 13, 1945, and the following day a biopsy was made of each testis The pathologic report revealed that the tubules were essentially negative except for slight mitotic activity A normal number of spermatids and spermatozoa were present It was thought at this time that a bilateral exploratory operation with a possible bilateral vaso epididymostomy should be done

The patient was readmitted to the hospital and on August 30, 1945 surgical exposure of the right scrotal contents and vascular pedicle was done The contents were investigated and the incision closed, the same procedure was carried out on the left side. Both testes and epididymes were of normal size and shape and there was no engorgement of the latter No structure was found resembling the vas in either scrotal compartment Plastic surgery was not possible for his azoospermia He was discharged from the hospital after the incisions had thoroughly healed The diagnosis was bilateral congenital absence of the vas deferens

Case 2 A 27 year old white man was married in February 1943 Contraceptives were used only the first 2 years of their marriage The patient had always enjoyed good health except for an injury to the left testis at the age of 12 This accident happened while he was riding horseback and the following day the left testis became very painful and swollen Gradually the swelling subsided and later this testis became very small In February 1945 the patient was examined by his local physician and a semen sample at this time revealed an absence of sperm He then was placed on 1 cc or 500 i u of antuitrin S every 3 days for 3 months without effect Examination of the semen on September 6 and 12, 1945, by another physician was also negative for spermatozoa

The patient was seen on December 27, 1945, in the urologic department of the Lahey Clinic Physical examination at this time revealed that the patient apparently was normal, weighed 165 pounds and was 6 feet tall The blood pressure was 122 mm systolic and 80 mm diastolic, the pulse 72 with normal rhythm, and the temperature was 98 4 F Examination of the genitalia revealed a small atrophied left testis and no vas deferens could be palpated The right testis was normal but the epididymis seemed to be swollen or enlarged with no palpable vas deferens in the cord The prostate gland was normal in size and shape and a smear in the wet state revealed normal elements The remainder of the physical examination was normal The urine had a specific gravity of 1 025, it was negative for both sugar and albumin, and the sediment was microscopically negative

On March 7, 1946, at the hospital, a biopsy on the right testis was reported to show "a relative decrease in spermatogenesis"

The patient was readmitted to the hospital on April 15, 1946, for a right exploratory operation or a possible right vaso epididymostomy The right scrotal contents and vascular pedicle were thoroughly investigated The right testis was normal but the epididymis was about twice normal size with dilatation of the tubules, giving a picture of "miniature brain convolutions" No vas deferens was found coming from the epididymis or in the vascular pedicle. The hospital convalescence was uneventful. The diagnosis was congenital absence of the right vas deferens with marked dilatation of the epididymal tubules, and traumatic atrophy of the left testis.

Case 3. A 38 year old man was seen because of enlargement of the left testicle and inability for his wife to become pregnant. The past history was essentially negative. Physical examination revealed a normal right testicle, but there was a dilatation or enlargement of the left epididymis. The patient refused to obtain a masterbated or condom specimen because of religious beliefs.

Intravenous pyelograms showed an absent or nonfunctioning left kidney. Cystoscopy disclosed an absent left ureteral orifice and left part of the trigone. At the insistence of the patient, the scrotum was explored and revealed a normal left testicle with a dilated epididymis. It narrowed at its terminal end and faded into an ill-defined fascial plane.

A final diagnosis was made of a congenital absence of the left kidney, ureter, and left horn of the trigone accompanied by an absence of the left vas deferens with marked dilatation of the epididymal tubules.

COMMENT

Case 1 had congenital absence of the vasa deferentia with an otherwise normal genital system. The patient had had a very mild case of uncomplicated gonorrhea. There was no history of epididymitis or other inflammatory conditions of the conduction system of the genitalia for this could not have happened by direct extension because of the absence of a passageway for the infection to travel. A biopsy revealed that the tubules were negative except for slight mitotic activity, and a normal number of spermatids and spermatozoa were found.

Case 2 is a case of complete absence of the right vas deferens and old traumatic atrophy of the left testis. The left vas deferens was not explored but it would not have been surprising, from the physical examination, to find none on this side. The biopsy showed only a relative decrease in spermatogenesis.

Case 3 had a complete absence of the left kidney, ureter, left horn of the vesicular trigone and vas deferens.

In reviewing all the reported cases it appears that the testes were not absent in any of the cases. Embryologically, the vas deferens is formed from the caudal end of the wolffian duct and the testis is formed from the genital ridge along the medial surface of the mesonephros proper. It may now be seen that the absence of the vas deferens does not predispose to the absence of the testis or epididymis on the same side.

In 7 cases there was an absence or a rudimentary seminal vesicle and probably more of this region had been explored on the surgical cases. This was the most common anomaly occurring in conjunction with absence of the vas deferens. Embryologically, the seminal vesicle is formed by an evagination of the caudal part of the wolffian duct. If there is aplasia or degeneration of this part of the wolffian duct, the seminal vesicle will fail to form.

In 3 of the reported cases there was an absence of the kidney on the same side in conjunction with congenital absence of the vas deferens The true kidney, metanephros or third kidney, has a double origin The secreting system, including Bowman's capsule with the glomerulus, the ascending and descending loops of Henle, and convoluted tubules, arises from a condensation of a group of cells in the nephrogenic fold The collecting system, including the tubules, calyces, pelvis and ureter, arises from an outgrowth from the lower end of the wolffian or mesonephric duct If there is a deficiency of the wolffian duct, therefore, it may cause an absence or aplasia of the kidney and vas deferens on the same side

Spermatogenesis and secretion of the male sex hormone take place even in complete absence of the vasa deferentia Spermatogenesis was found in the 2 cases of Oleson and the 3 cases reported in this paper The reported cases were males with normal secondary characteristics In cases of azoospermia, the vas deferens should be thoroughly investigated for obstruction or congenital absence

SUMMARY

Congenital absence of the vas deferens may occur unilaterally or bilaterally, with or without the absence of the corresponding seminal vesicle

Bilateral congenital absence of the vas deferens is a rare cause of sterility in the male

Absence of the vas deferens may occur with the absence or aplasia of the kidney on the same side but they have no effect on the formation of the testis

Spermatogenesis and formation of the male sex hormone occur and may proceed normally, even with absence of the vas deferens

The author is grateful to Dr Earl Ewert of the Lahey Clinic for the availability of the clinical records of cases 1 and 2 while he was associated with him

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ACTINOMYCOSIS OF THE TESTICLE

ROBERT H HEPBURN

Four cases of actinomycosis of the testicle have been reported to date Because of the apparent rarity of the disease it seems worth while to report a fifth case seen recently at the Hartford Hospital

C R, aged 79, a retired rose gardener, was admitted in almost complete urinary retention July 23, 1948, to the private service of Dr Thomas N Hepburn For many years the patient had noted gradually diminishing force to the stream associated with increasing nocturia and frequency There had also been increasing deafness for several years with almost total blindness from bilateral glaucoma for which operations had been done some fifteen years prior to this admission For at least 28 years, since 1920, there had been intermittent swelling of the left testicle approximately every few years The youngest of the patient's 3 children was about 21 years old at the onset of this difficulty Under Dr Thomas Hepburn's supervision, the patient's daughter, a graduate nurse specializing in urological nursing, successfully carried her father through these episodes by means of scrotal support and Sitz baths The daughter states that the testicle became "very large" during one flare up in 1924 but since then the swellings have been small with rapid subsidence For several years prior to admission there had been no swellings though the left testicle had remained slightly larger than the right As a rose gardener the patient had worked with sheep manure all his life and, according to his daughter, the patient "when a youngster in Redding, Connecticut, picked huckleberries in Sammy Osborn's sheep pasture The Osborns had a large sheep herd " The patient, whose memory is not reliable, states that it is possible the testicular swelling went back to childhood but he cannot recall for certain and the wife and daughter have no knowledge of it before 1920

Physical examination showed a well developed and nourished old man in moderate discomfort from a distended bladder The prostate was twice normal size with some firmness in the left portion near the bladder suggestive of carcinoma The left testicle was slightly larger than the right There was a 1 0 by 1 0 cm pedunculated fibroma in the skin of the midback and a 6 0 by 8 0 cm lipoma on the right upper arm posteriorly The pupils were irregular and fixed Vision in the right eye was absent and in the left markedly diminished Hearing was poor bilaterally The chest showed some emphysema, there were dry coarse râles at the right base A grade 2 apical systolic murmur was transmitted to the aortic area There was considerable sclerosis of the radial arteries

Laboratory examination revealed an acid phosphatase of 1 0, hematocrit 46, nonprotein nitrogen 31 X-ray examination of the chest showed that "except for slight exaggeration of the bronchovascular structures in the posterior lung fields seen on the lateral view, the lungs are clear The aorta is tortuous and there is calcification in its walls "

After 4 days' bladder drainage by inlying Foley catheter, cystoscopy was done, demonstrating clinically a benign prostatic enlargement of moderate dimensions. Four days later the left testis became acutely enlarged and inflamed with only slight subsidence during the next 11 days. On the nineteenth day perineal prostatectomy and left orchiectomy were carried out by Dr. Thomas Hepburn.

Pathological report: "Sections of the prostate show typical nodules of benign overgrowth. In one focus there is a zone of acute inflammatory infiltration.

"The testis is 9 cm. in greatest diameter. The normal tubular substance is replaced by a gray firm white substance which apparently infiltrates but does not invade the capsule. Sections of the testis show extensive suppurative inflammatory process with acute and chronic inflammatory exudate present. In the center of the abscess-like formations are typical actinomycosis colonies. Extensive acute and chronic inflammatory infiltration extends throughout the testicle tissue around the actinomycosis colonies." Unfortunately no note was recorded as to the condition of the epididymis but it was not noted to be enlarged at surgery.

The scrotal wound healed rapidly and uneventfully. No drugs of any kind were used.

PREVIOUS CASE REPORTS

Mention of these is made in some detail since there are but 4 and they help round out the picture to date.

1898. Dr. Eustace's patient, aged 35, seen in England, had a "swelling on the left cord" of 3 months' duration. He had always lived in the country but "had never farmed or was in any way connected with stabling or farmyard work." The youngest of his two healthy children was 8 years old. Examination showed 1) a hard cylindrical swelling, painless and nontender on the left cord about the size of a hazelnut and situated about 1 inch from the external abdominal ring, 2) a small hydrocele of the cord, 3) general enlargement of the testicle but chiefly of the globus minor. There were no enlarged lymph nodes. Rectal examination was normal including prostate, vesicles, base of bladder. Remainder of examination normal. Presumptive diagnosis: Some chronic inflammatory process, probably tuberculosis. Treatment: Excision of testis and cord. "Two sections of the growth exhibited the typical appearance of actinomyces bovis." At follow-up 2 months after operation the wound was well healed. Medication: potassium iodide grains 5 t.i.d. for 3 months postoperatively. No mention of where the sections were from but in the author's opinion this was the first reported case of actinomycosis of the testis. It was not stated whether the cord was also involved but by implication it was.

1925. Sanford and Voelker's patient was very briefly mentioned in their review of actinomycosis in the United States. He was a 47 year old minister from Holland, seen in 1921 at the Mayo Clinic. He had had 10 months of unstated symptoms and the only other comment was that the pathological diagnosis was made after orchidectomy.

1945. Schneider reported a man seen on the Tulane urological service, Charity Hospital, New Orleans, Louisiana The patient was an 80 year old colored farmer admitted in acute retention He had had symptoms of prostatic obstruction for 1 year. Twelve children were living and well The genitalia were normal except for a slightly nodular prostate, enlarged grade 1–2 plus, soft, movable, without fixation Seminal vesicles were not palpable Teeth carious Aortic diastolic, mitral systolic murmurs Except for slight albuminuria and pyuria the remainder of the routine laboratory examination was negative A plain x-ray of the abdomen was normal A cystogram showed evidence of prostatic enlargement

An inlying catheter was introduced Because of marked urethritis and balanoposthitis a suprapublic cystostomy and dorsal slit were done 3 days later. Five days following this a right epididymitis occurred but subsided rapidly treated "in the usual manner" By transurethral resection 46 gm of prostatic tissue were removed and reported to show adenocarcinoma microscopically Accordingly a left subcapsular orchidectomy was done and a similar operation begun on the right Because of a nonfluctuant pale yellow abscess about 8 by 10 mm in the lower pole an orchiectomy was done "Section shows nodular areas of pale gray and yellow tissue occupying the peripheral half of the testicle. Nodules are confluent and measure individually 2 mm in diameter The hilus is normal except for moderate fibrosis The tubules do not string Epididymis is firm but shows no evidence of inflammation on section. Microscopic diagnosis: Actinomycosis" The section shown had the same outstanding characteristics as that in figure 1, *A* Convalescence was uneventful No follow up given

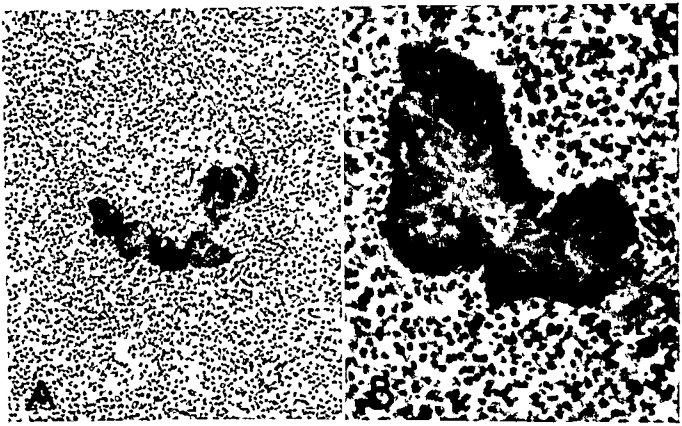

FIG 1 Testis Microscopic Sections, Hartford Hospital Case

1946 Baker and Ragins reported a 77 year old machinist with a 1 month's history of frequency and low back pain The prostate, clinically carcinomatous with increased firmness and fixation of the right lateral lobe, was proved to be so on microscopic section of 9.5 gm. tissue removed transurethrally. On the thirteenth postoperative day acute bilateral epididymitis developed. It subsided rapidly and bilateral orchiectomy was done 2 months after the resection. Both testes and some of the cords were removed. Convalescence was uneventful. Pathological report: "The tunica vaginalis of the right testicle was loosely adherent to the tunica albuginea and the testicle measured 5 by 3.5 by 3 cm. The section surface was brownish gray and studded by numerous abscesses which were filled with a greenish gray purulent material emitting a musty odor. The right epididymis showed no gross abnormal findings. The left testicle measured 4 by 3 by 2 by 2 cm. The parenchyma was light tan gray and atrophic. The left epididymis showed no gross changes. Microscopic examination revealed distinct ray-shaped granules. Because of the typical radiating fungus with bulbous mycelia at the periphery, the organism may be considered actinomycosis bovis (Wolf-Israeli type)." The sections appeared essentially like figure 1, *A*.

CONCLUSIONS

Evidently a chronic recurrent orchitis may be due to actinomycosis. The infection may have intermittent exacerbations for decades without leading to the fistulas so common in tuberculosis of the testicle. Between exacerbations the testis may appear about normal clinically. There may also be no history or symptoms of orchitis in testicular actinomycosis. There need not be clinical actinomycosis elsewhere in the body. Surgical removal of the involved testis, epididymis and adjacent cord has resulted in cure without the use of sulfonamides or antibiotics. This might be expected because of failure of the organism to penetrate the tough tunica albuginea so that the disease has probably been totally eradicated by surgical excision alone. The testis as opposed to the epididymis would seem to be more susceptible.

SUMMARY

A fifth case of testicular actinomycosis is presented. The literature is reviewed and a few tentative conclusions made. It was surprising to me to note the clinical benignity of the disease to date together with its ready cure by surgery alone. It is to be hoped that this communication will emphasize another differential suspicion for physicians to worry over when they contemplate the orchid, be it swollen or not.

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THE SURGICAL TREATMENT OF ELEPHANTIASIS

D F McDONALD[1] AND C HUGGINS

From the Division of Urology Department of Surgery, the University of Chicago, Chicago

This report is concerned with a surgical approach to the problem of genital elephantiasis which has been used in this clinic since 1941 It depends upon the production of a new avenue of lymph flow from the diseased parts, by means of a large anastomosis of the subcutaneous tissues of the scrotum and thighs

In 1943, H H Young presented a case of paraffinoma of the scrotum with elephantiasis in which repeated resection of diseased tissues resulted in alleviation of the condition G Livermore in considering the etiology of non filarial genital elephantiasis indicated that blockage of lymphatics of the scrotum and penis due to cicatricial contraction following chancroid, tuberculosis, syphilis, trauma, excision of lymph nodes, herniorrhaphy or streptococcus lymphangitis was the cause of the genital edema In discussion of the above papers Reed Nesbit suggested that an anastomosis of the scrotum to the thigh similar to the procedure used in the Torek operation might allow drainage through the lymphatics of the thigh

W S Halsted reported that in dogs division and resuture of all the tissues of the thigh except the femoral artery, nerve and vein, and the femur was attended by a considerable edema below the suture line After 1 week the edema completely subsided This showed that the lymphatic circulation could re establish itself through a scar in one week or less In this same paper Halsted reported a case of genital elephantiasis following excision of inguinal nodes which was chronic in its course This patient had recurrent attacks of chills and fever associated with redness and increased swelling of the genital area about every 6 months for 38 years

In elephantiasis involving the male genitalia caused by lymphatic obstruction, edema is confined to the superficial tissues of the penis and scrotum while those of the thigh are commonly uninvolved The principle of the operation which we carried out is the construction of new lymphatic pathways to allow the scrotal lymph to become absorbed via the uninvolved thighs Technically this was done by constructing a bridge of generous size between scrotum and thigh utilizing the method of the first stage of the Keetley and the Torek procedure

The bridge is intended to be permanent It was found that this treatment was well tolerated by the patient in whom it caused neither discomfort nor disability

CASE REPORTS

Case 1 G H F, a 37 year old oil driller, first seen February 5, 1941, complained of swelling of the genitalia of 8 years' duration He gave a history of bilateral painless inguinal swelling which was drained surgically Following removal of the drains the scrotum and penis became swollen to 3 times normal

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[1] Present address University of Washington Department of Surgery, Seattle, Washington

size. The patient also stated that about once a year the genitalia became very hot, painful and red and enlarged to the size of the human head. After about a week the swelling would subside to its original 3 times normal size. He also stated that 8 years ago he had had a positive blood test for syphilis and had received arsenical and bismuth injections regularly. The scrotum measured 8 by 6 cm. and the penis was 5 cm. in diameter (fig. 1, *A*). The scrotal and penile skin were thickened, reddened and warmer than the skin of the abdomen. There were scars in both inguinal regions and at the left inguinal ring there was a 1 cm. hard, non-tender mass. The Frei test was positive. On March 20, 1941, a 3 inch elliptical incision was made in the skin of the left thigh and a segment of skin was removed. A corresponding incision was then made in the scrotum. The scrotal skin was markedly thickened and fibrosed and oozed a clear fluid. The posterior layer of the scrotum to thigh anastomosis was made with a No. 1 chromic catgut and the anterior layer was closed with silk. A similar procedure was then done on the right side. There was slight decrease in size of the scrotum at the time of discharge from the hospital on April 4, 1941. By April 17, the scrotum had decreased to normal size and the patient stated that he felt better than he had felt in years. On June 23, 1941, the patient said that he had had some swelling and redness of the scrotum which had been controlled by sulfathiazole. On December 8, 1941, the patient said he had been well since September and the scrotum was normal in size and consistency. The distal two thirds of the penis remained somewhat edematous. On April 16, 1942, the condition of the genitalia was still good (fig. 1, *B*). On April 29, 1943, the patient stated that except for several light attacks of scrotal swelling the condition remained good and he was able to carry on a normal, active life.

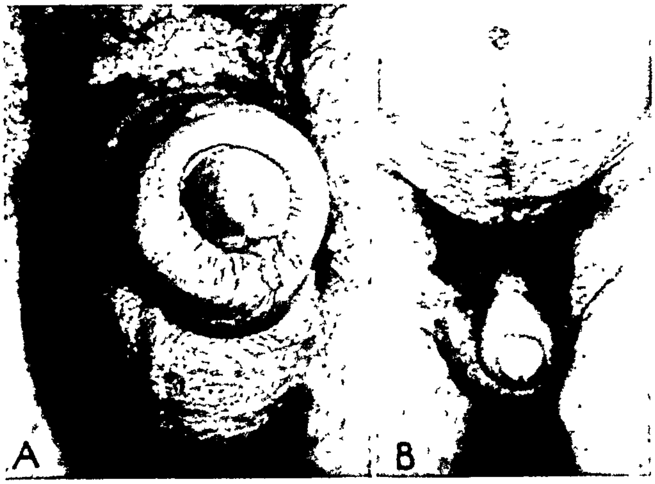

FIG. 1. Case 1. *A*, non-filarial genital elephantiasis before treatment. *B*, 1 year after bilateral scrotum to thigh anastomosis.

Case 2. O. H. L., a 47 year old railroad man, complained of gradually increasing swelling of the scrotum and penis in the past 9 years. He stated that, in 1938, he developed a painful swelling of the shaft of the penis which completely disappeared. Since that time he noted progressive increase in the size of the

Many resectionists will find it advantageous to use the smaller sized instruments in patients who have urethras which do not easily accommodate the standard sized sheath. Heretofore, we have found it desirable to perform meatotomy in about 35 per cent of cases, and perineal urethrotomy in 20 per cent in the avoidance of urethral trauma. Using the No. 26 instrument, we have found little difference in the operating time when resecting glands of moderately large size. We have employed the No. 24 instrument in a considerable number of cases and have been pleasantly surprised to find that glands of small or moderate size (up to a yield of 40 gm.) have been easily and expeditiously removed with the instrument.

Most resectionists of average skill will probably be able to employ the No. 26 instrument in the majority of cases and will no doubt use the No. 24 more often than the standard sized resectoscope, thereby eliminating many of the risks of urethral trauma during transurethral prostatic resection.

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SCIENTIFIC PROGRAM, ANNUAL MEETING, SOUTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION, EDGEWATER PARK, MISSISSIPPI, FEBRUARY 1, 2, 3, 4, 1950

THURSDAY, FEBRUARY 2

9–12 A.M.

THE FOLEY LUMBAR URETEROLITHOTOMY—AMPLIFICATION OF ITS USE. Dr. Bruno Barelare, Birmingham, Alabama.

NEPHROCOLOPEXY, TRANSLUMBAR. Dr. Francisco Barquin, Havana, Cuba.

THE UTILIZATION OF THE FATTY CAPSULE OF GEROTA IN PYELOURETEROPLASTY. Dr. I. G. Duncan, Memphis, Tennessee.

Dr. William Engel, Cleveland, Ohio, Guest Speaker. Selected Subject.

VESICO-COLIC FISTULA—WITH CASE REPORTS. Dr. N. L. Bosworth, Lexington, Kentucky.

1:30–3:00 P.M.

URETERO-SIGMOIDOSTOMY: A COMPARATIVE STUDY OF TECHNIQUES. Dr. C. A. Fort, Atlanta, Ga.

Dr. Carl Rusche, President, American Urological Association. Selected Subject.

URETERO-ARACHNOID ANASTOMOSIS FOR COMMUNICATING HYDROCEPHALUS. Dr. John E. Dees, Durham, North Carolina.

3:00–5:00 P.M.

Moving Pictures and Scientific Exhibits

FRIDAY, FEBRUARY 3

9–12 A.M.

ADENOCARCINOMA OF THE PROSTATE WITH METASTASIS TO THE TESTICLE. Dr. Allen C. Bradham, Anderson, S. C.

SOME UROLOGIC COMPLICATIONS OF PREGNANCY. Drs. Coplan, Woods & Melvin, Miami, Fla.

ELECTROSURGICAL TECHNIQUE—ITS IMPORTANCE IN TRANSURETHRAL RESECTION OF THE PROSTATE. Dr. James H. Semans, Atlanta, Ga.

Dr. George Cahill, New York, N. Y., Guest Speaker. Selected Subject.

UROLOGIC PROBLEMS IN CHILDREN. Dr. John Dougherty, Knoxville, Tennessee.

1:30–4:00 P.M.

Past President's Address, Dr. Harold P. McDonald, Atlanta, Georgia. EVOLUTION OF PROSTATIC SURGERY.

The Ballenger Memorial Lecture, Dr. Thomas Findley, New Orleans, Louisiana. SOME HEMOSTATIC FUNCTIONS OF THE KIDNEY.

PHEOCHROMOCYTOMA—REPORT OF A CASE. Dr. Frank J. Pyle, Orlando, Florida.

MANSON'S SCHISTOSOMIASIS OF LEFT ECTOPIC KIDNEY. Dr. Luis A. Sanjurjo, Puerto Rico.

SATURDAY, FEBRUARY 4

9:00–11:30 A.M.

GROSS HEMATURIA DUE TO DICUMEROL. Dr. Linus W. Hewit, Tampa, Fla.

USE OF ANTI-HISTAMINE DRUG PROPHYLAXIS AGAINST DIODRAST REACTIONS. Dr. Paul L. Getzoff, New Orleans, La.

VESICAL EVIDENCE OF POSTERO-LATERAL SPINAL COLUMN DISEASE. Dr. Robert Lich, Jr., Louisville, Kentucky.

GENITO-URINARY TRACT INFECTIONS; EXPERIENCES WITH IN VITRO SENSITIVITY TESTS IN CHOICE OF ANTIBIOTICS. Dr. Joseph C. Hayward, Orlando, Fla.

scrotum and penis and thickening of the skin. In 1945, the patient began to have attacks of chills and fever associated with redness, tenderness and increased swelling of the penis and scrotum which would last several days. The patient said that after each attack the scrotum decreased a little in size but never quite down to the size immediately preceding the acute attack. These episodes occurred every 6 to 8 weeks and made it impossible for the patient to work regularly. The past history was non-contributory except for bilateral inguinal herniae since 1934 for which the patient wore a double truss. There was no history of venereal disease.

When first seen, on May 23, 1947, the scrotum was enlarged to the size of a grapefruit. The skin was thick and edematous, but there was no pitting on pressure. The right lateral aspect of the shaft of the penis was marked by a soft swelling about 3 by 5 cm. which caused angulation of the penis to the left. There were bilateral direct inguinal herniae. There was a lipoma 15 by 25 cm. over the crest of the ilium. The remainder of the physical examination was negative. The Kahn test on the blood was negative. There was a leukocytosis of 12,000. The urine was normal.

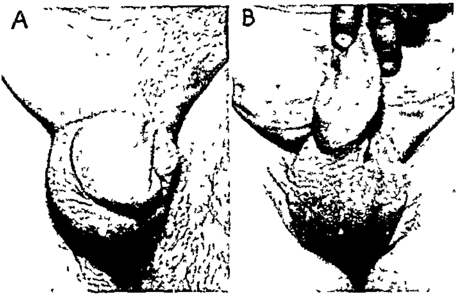

FIG 2. Case 2 *A*, non-filarial genital elephantiasis before treatment. *B*, 1 year after bilateral scrotum to thigh anastomosis.

On October 9, 1947, the patient developed acute swelling, tenderness and redness of the scrotum with chills and generalized malaise. On October 14, 1947, he was admitted to the Billings Hospital. The scrotum was red and tender. There was an ulcerated area in the concavity of the angulated penis (fig. 2, *A*). His temperature was 37.4 C. Penicillin 30,000 units every 3 hours, and sulfathiazole 0.5 gm. 4 times daily were given. The acute inflammation subsided completely in 5 days and, on October 20, a bilateral herniorrhaphy was performed. One week later, a bilateral scrotum to thigh anastomosis was made. Four-inch incisions were made in the thigh and scrotum and anastomoses similar to the Torek procedure were made bilaterally. Biopsy of the scrotum showed that the skin was 5 mm. thick. Microscopically there was a marked increase of dense collagen in the skin and subcutis. There was dilatation of the superficial lymphatics, but there was very little edema. Lymphocytes and macrophages were found in abundance around vessels and sweat glands and in the dilated lymphatics. Diagnosis was chronic lymphangitis, edema and sclerosis (scrotal elephantiasis; non-parasitic). The patient had a satisfactory afebrile postoperative course. The wounds healed slowly with some clear fluid drainage. He was discharged from the hospital on November 2, 1947. By November 22, the incisions were completely healed. On December 2, 1947, the scrotum had decreased 20 per cent and penis 10 per cent. On March 29, 1948, the scrotum was completely soft and normal in size, although the penile edema had not appreciably changed. The patient was at work with no disability due to the scrotal-thigh anastomosis. He had not had any attacks of erysipelas since the operation and felt well. On November 3, 1948, the patient said he had continued in good condition without discomfort and had satisfactory sexual relationships. The scrotum and penis appeared normal (fig. 2, *B*).

DISCUSSION

Surgical by-pass of the obstructed lymphatics solves the scrotal edema problem, but slight penile edema persists. The penile edema, according to the patient, decreases during erection of the penis and intercourse is satisfactory. No limitation of activity results from the bilateral scrotum to thigh anastomosis.

SUMMARY

A surgical method of producing a new avenue of lymph flow from the scrotum is described and 2 cases in which it has been used in treatment of non-filarial genital elephantiasis are reported.

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AN IMPROVED RESECTOSCOPE IN SIZES 24, 26 AND 28 FRENCH

REED M NESBIT

From the Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan

In 1938 I recommended that structural changes in the McCarthy resectoscope be made which would make its one-handed manipulation possible, and to that end submitted sketches of the proposed instrument to Mr Frederick Wappler The modified resectoscope was constructed in accordance with the original specifications except that roller bearings were not incorporated in the carriage to ensure smooth operation This instrument was originally made in two sizes, the standard 28 F, and a larger size, 33 F It was hoped that the larger instrument, when introduced by way of perineal urethrotomy would speed up the resection of large prostates, but this did not prove to be true because it was held tightly in the menbranous urethra in many patients thus reducing its maneuverability, so its use was abandoned

The sliding bearings of the early models caused many of the instruments to operate with more or less friction which interfered with efficient manipulation In our own hands graphite in oil was used to eliminate the areas of friction and we have employed the modified resectoscope for many years in the belief that it is easier to operate than the original McCarthy instrument Furthermore, time and experience have proved the advantage of rectal palpation during transurethral prostatic resection

The war delayed necessary and desirable improvements of this instrument but they have finally been made after the construction of many working models (figs 1 and 2) The present model has been used extensively by me and the various members of my staff, and it appears to be an efficient and sturdy instrument. Mr Frederick J Wallace and his research engineers at A C M I deserve commendation for their patience in the matter of permitting numerous changes in working models of the instrument, which have been made at the insistence of the author and which have held up production for over a year, for it is my belief that successful transurethral prostatectomy can only be performed with instruments that can be operated with delicacy, precision and perfect balance

The working element of this instrument is fitted with roller bearings which insure a smooth and easy excursion of the carriage, and utilizes the 68A for-oblique lens system There are three sizes of sheath—24, 26 and 28 F with corresponding sized loops, all of which are adaptable to use with the one working element It is recommended that the pistol grip handle, previously incorporated in the modified resectoscope, not be employed in the present model, in the interests of increased flexibility of operation for we believe that this surgical instrument is best handled by fingertip grasp In the past, when our residents have begun to learn resection techniques using an instrument with a handle, they have displayed a tendency to "freeze" onto it like a student pilot to his airplane stick, so the handle has long since been abandoned as part of the equipment

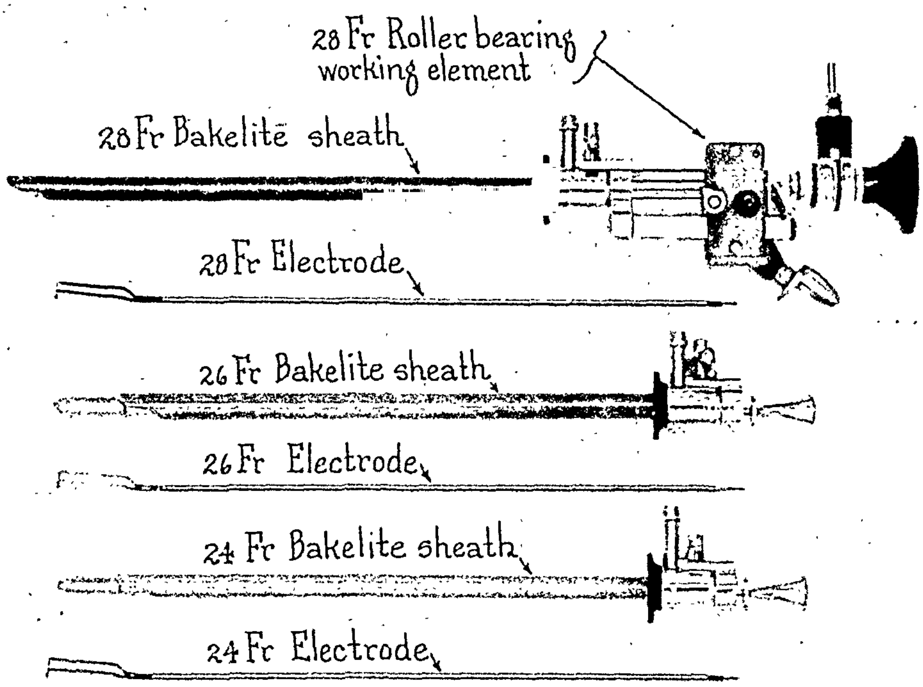
28 Fr Roller bearing working element
28 Fr Bakelite sheath
28 Fr Electrode
26 Fr Bakelite sheath
26 Fr Electrode
24 Fr Bakelite sheath
24 Fr Electrode

FIG. 1

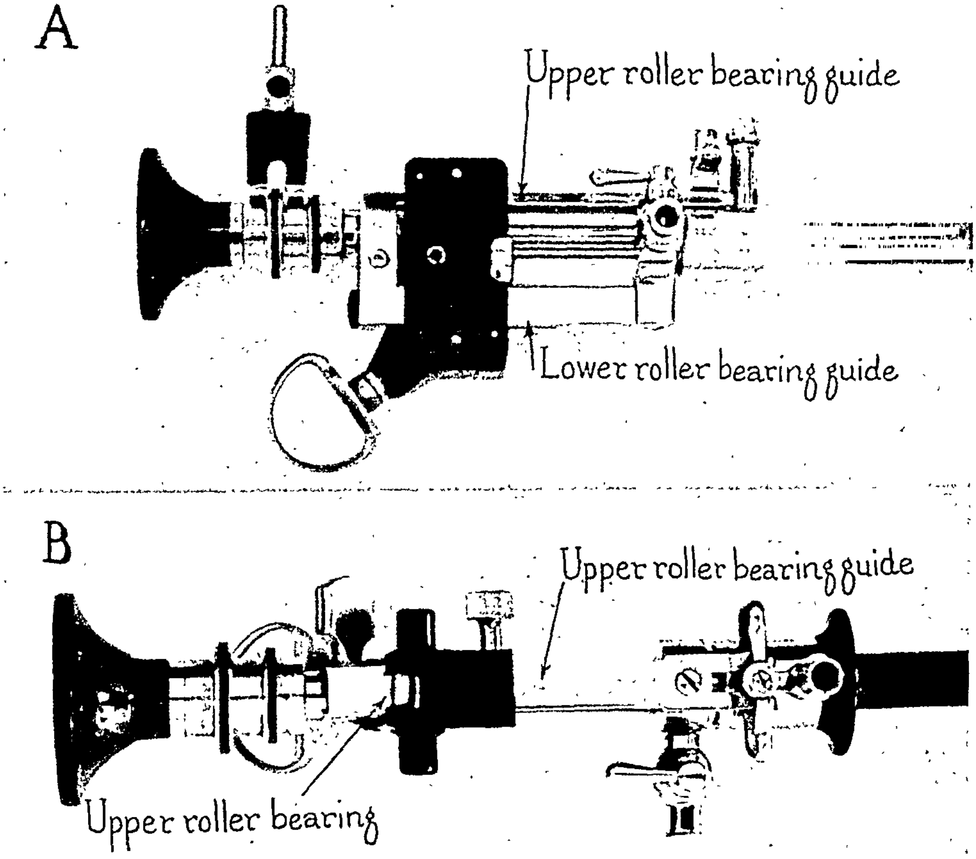
A
Upper roller bearing guide
Lower roller bearing guide
B
Upper roller bearing guide
Upper roller bearing

FIG. 2

Choice in Excretion Urography

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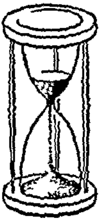

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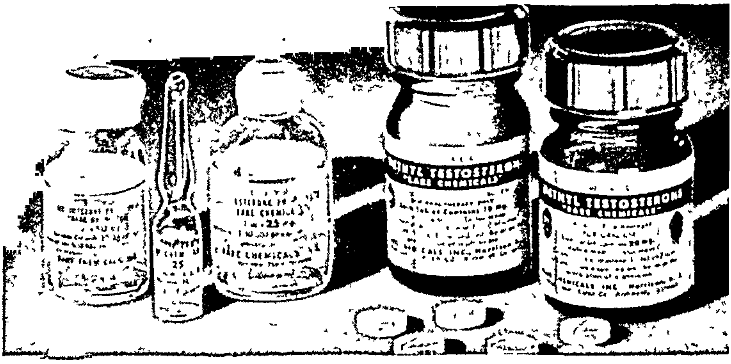

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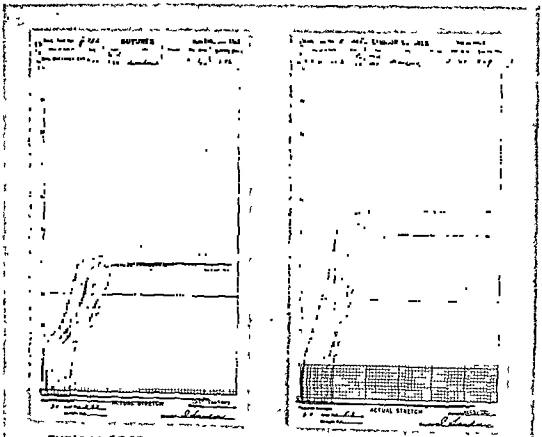

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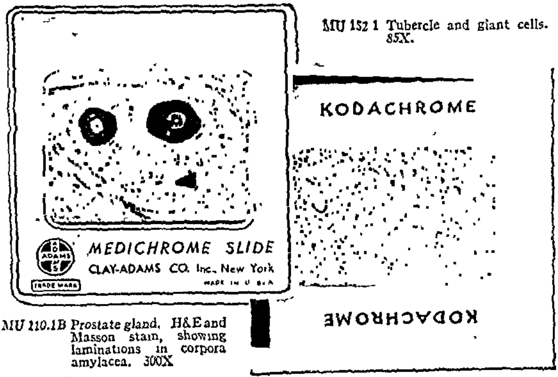

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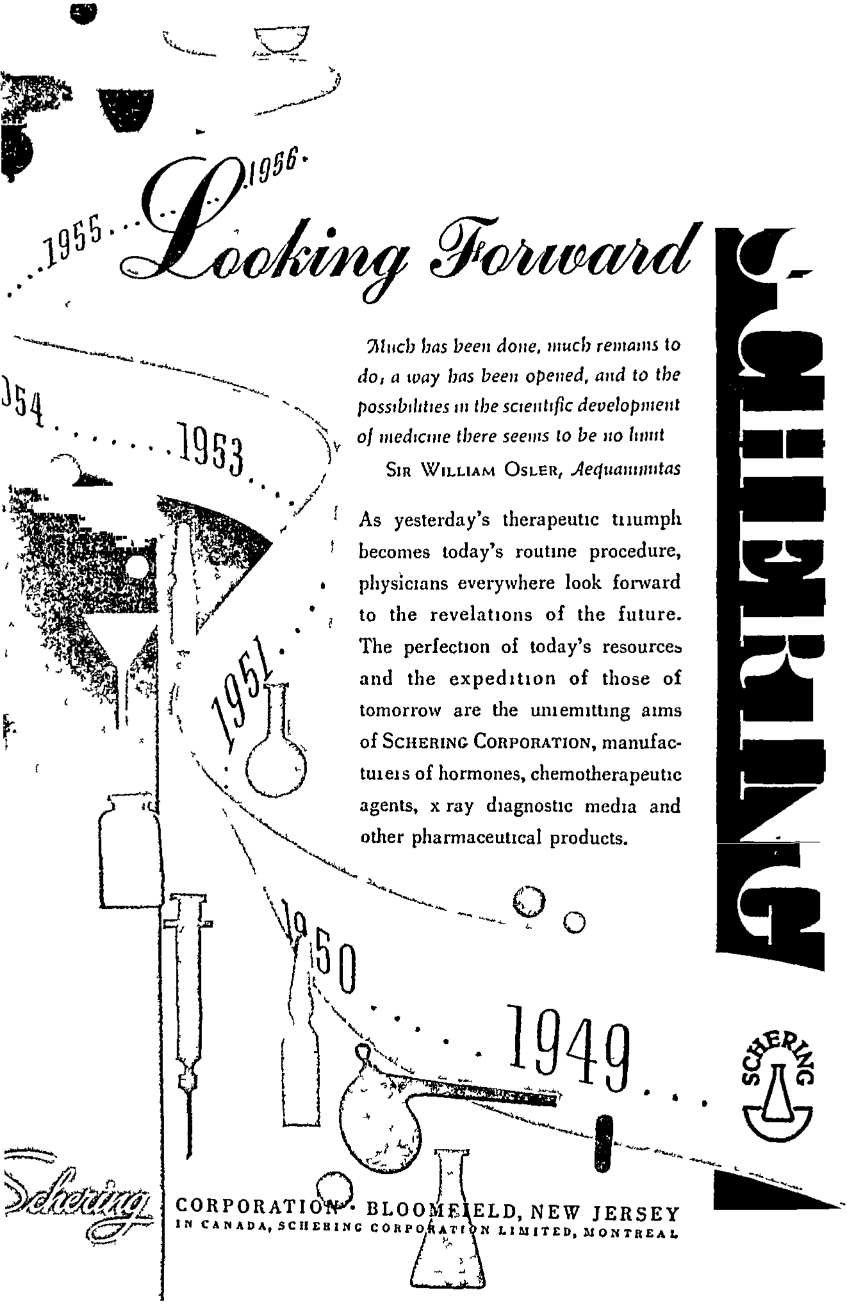

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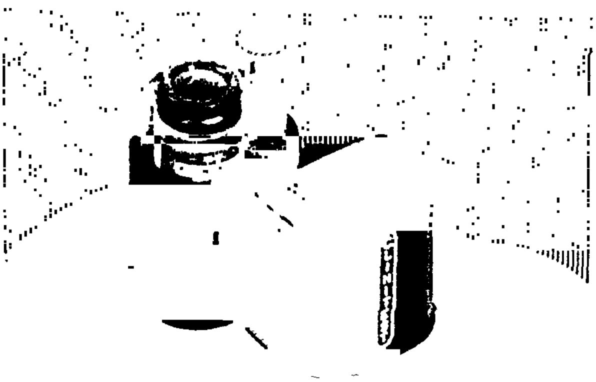

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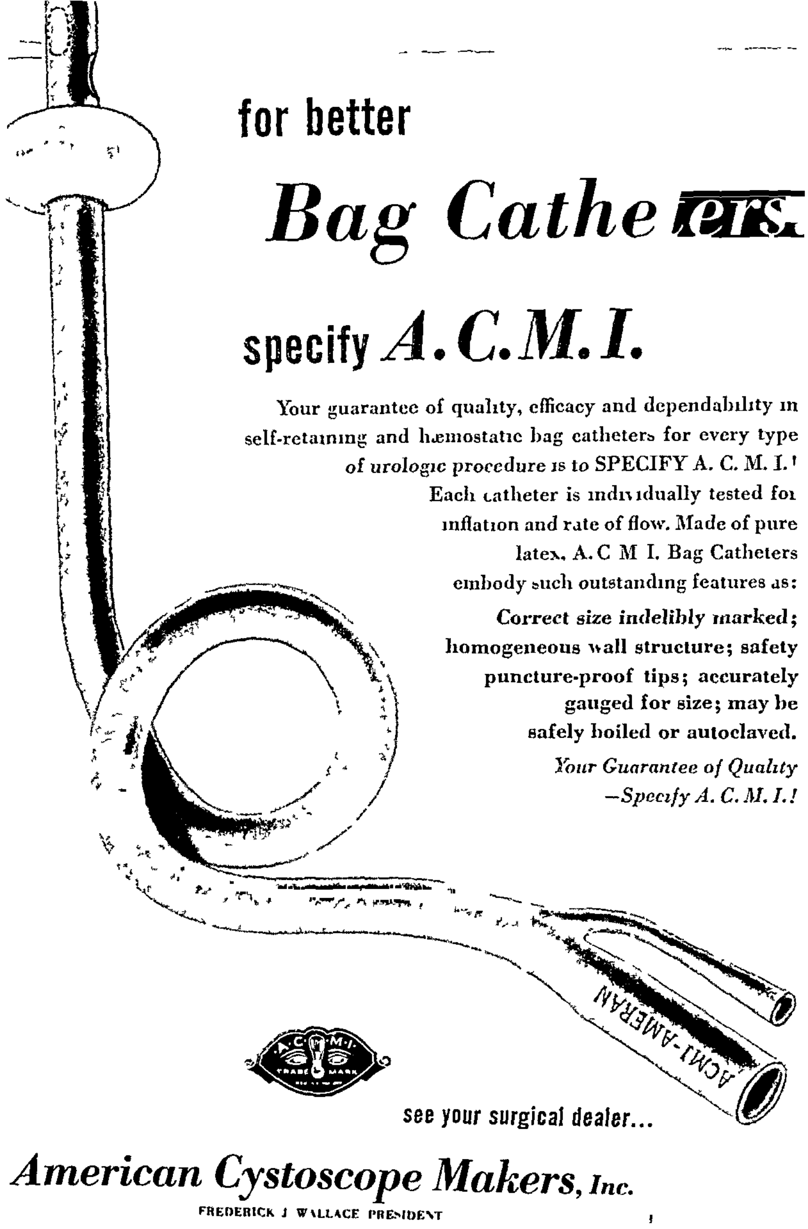

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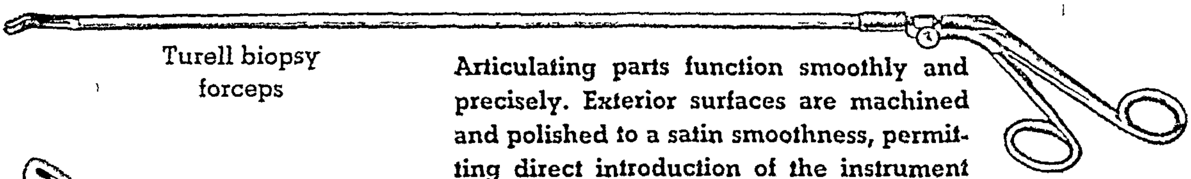

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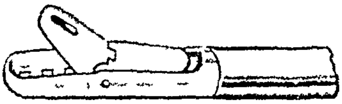

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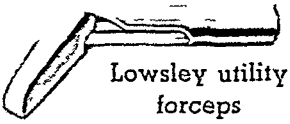

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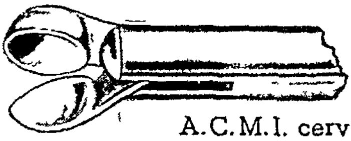

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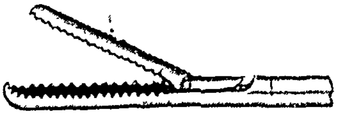

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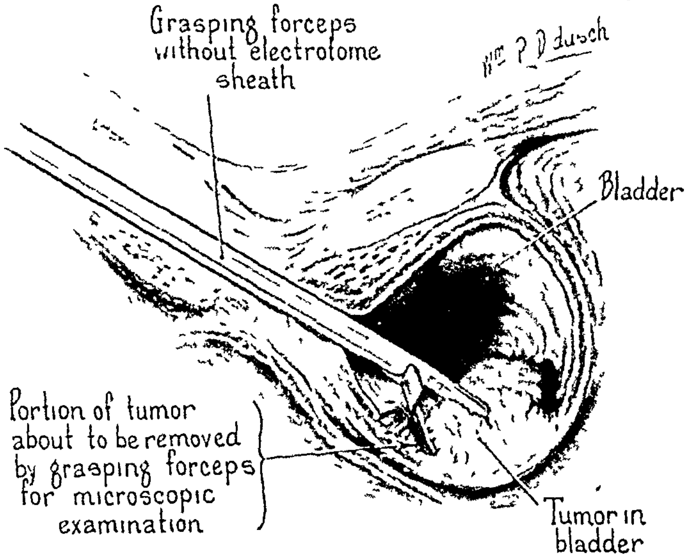
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RENAL INFARCTION: A CLINICAL AND POSSIBLE SURGICAL ENTITY[1]

FRANCIS C. REGAN (BY INVITATION) AND E. GRANVILLE CRABTREE

Septic arterial infarcts of the kidney, venous infarction, infarction from renal vessel injury, and sterile infarction are well known to the pathologist from autopsy material. The urologist is familiar with scarring of the kidney seen at operation, a testimonial to a bygone injury. Yet, in the great majority of instances, where infarction has been encountered clinically, nephrectomy has been done, based on erroneous diagnosis, and the condition has not been recognized even from the appearance of the kidney in the wound. There are sufficient clinical data produced by infarction to make a diagnosis in acute stages of the injury to the kidney, but the information appears to need distribution.

An attempt is made in this contribution to indicate types of infarction which may be encountered and their immediate and remote effects on the anatomy and physiology of the kidney, to collect the reported cases, and to lay down the essentials of clinical diagnosis, both for the acute and the terminal states of the disease. Diagnosis may be suspected by the internist, confirmed by the pathologist after death, but the clinical diagnosis rests with the urologist if proper management in the living is to be made.

EXPERIMENTAL OBSERVATIONS

Litten[2] (1880) and Westerborn[3] (1937) have shown that temporary ligation of the renal artery for more than 1½ hours is followed by necrosis of all the elements of the kidney. The renal artery, ligated for less than 1½ hours, causes only edema and hyperemia of the kidney.

Foa[4] (1889) described the gross and microscopic changes of a renal infarct caused by permanent ligation of a branch of the renal artery. At first the color is reddish gray, the infarct stands above the surface of the rest of the kidney and the tubular epithelium is swollen and cloudy and shows disintegration of its nuclei. The glomeruli and blood vessels, aside from edema and diapedesis of red cells, appear normal. There is a red zone surrounding the infarct, between it and the normal tissue, caused by tremendous engorgement of the capillaries. After 3 to 4 days the infarct has a gray color, the surface is level with the rest of the kidney, and the boundary zone is less red and wider. The tubular epithelium has lost its architecture and appears as a hyaline or granular mass. Many of the glomeruli show partial or complete necrosis and there are thrombi in the smaller arterioles. After 8 to 15 days the infarct has become smaller in all dimensions and is retracted from the surface of the kidney. There is a progressive contraction so that at 1½ to 2 months there may be found, at the site of the infarct, only an umbilication of the renal capsule, the infarct itself being represented by a yellow, contracted zone in the cortex. Occasionally there is left, in place of the infarct, a deep and irregular cyst or cavity which is covered with fibrous tissue and surrounded by exuberant parenchyma. At times the infarct may be reduced to a small calcified mass.

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[1] Read at annual meeting American Urological Association, Buffalo, N. Y., June 30, 1947.

[2] Litten, M.: Untersuchungen uber den hemorrhagischen Infarkt und uber der Einwirkung arterieller Anaemie auf das lebende Gewebe. Ztschr. f. klin. Med., 1: 131–227, 1880.

[3] Westerborn, A.: Emboli in der Arteria renalis mit Bericht uber einen operierten Fall sowie uber experimentelle Untersuchungen daruber, wie lange die Blutzufuhr nach der Niere abgesperrt sein kann, ohne dass ihre Funktionsfahigkeit aufgehoben wird. Ztschr. f. Urol., 31: 687–708, 1937.

[4] Foa, P.: Uber Niereninfarkte, Experimentaluntersuchung. Beitr. z. path. Anat. u. z. allg. Path., 5: 277–289, 1889.

Litten[2] and Loomis and Jett-Jackson[5] (1942) describe cysts or cyst-like areas occurring in the healed infarct. Loomis and Jett-Jackson have shown that renal infarct produces a profound disturbance of the circulation of the kidney. This consists mainly of capillary anastomosis between the glomerular efferent vessels and between the capillaries of the cortex and the renal capsule. The volume and pressure of the blood flow in the neighboring areas are increased to the fullest extent possible. The tissue nearest to these areas may be fairly well preserved and show only slight atrophy. The tissue near the center of the infarct shows complete necrosis. In rare cases, where there is a perforating artery anastomosing with the capsular arteries, part of the renal tissue in the center of the infarct may be well preserved. The changes in the arterioles seen in the first 2 or 3 days after infarction are mainly edema of the vessel wall and infiltration of red blood cells. At 7 days, there is a proliferation of fibroblasts in the vessel wall and in the tissues around the vessel. At 14 days, there is a pronounced thickening of the intima and replacement of the muscularis with fibroblasts.

Thorel[6] (1896) believes that the reaction seen in the peripheral red zone is analogous to compensatory hypertrophy. As evidence of this he describes the microscopic picture of the enlargement of glomeruli and tubular epithelium and the dilatation of the medullary tubules and collecting ducts.

Belt and Joelson[7] (1925) ligated the anterior branch of the renal artery in dogs and then injected colored celluloid emulsion into the renal artery. At 2 days, only a few small vessels in the infarcted area were injected. At 3 to 14 days the emulsion appeared in many large and small vessels as well as some of the glomeruli. After 35 to 40 days the glomeruli and most of the smaller vessels failed to be injected.

Staehler[8] (1938) and Westerborn[3] both clamped the left renal artery in dogs for 2 or 3 hours. The plain x-ray taken a week later showed an enlarged, symmetrical kidney which was completely calcified. Plain x-ray 2 to 3 weeks later showed the kidney about normal size and calcification still present. One and one-half years later the kidney was a calcified mass the size of a walnut.

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[5] Loomis, D. and Jett-Jackson, C.: Plastic studies in abnormal renal architecture. An investigation of the circulation in infarcts of the kidney. Arch. Path., **33:** 735–769, 1942.

[6] Thorel, Ch.: Uber typische und Pseudoregeneration bei Niereninfarkten. Virchows Arch. f. path. Anat., **146:** 297–313, 1896.

[7] Belt, A. E. and Joelson, J. J.: The effect of ligation of branches of the renal artery. Arch. Surg., **10:** 117–149, 1925.

[8] Staehler, W.: Zur Klinik der ortlich begrenzten Zirkulationsstorungen der Niere. Beitr. z. klin. Chir., **167:** 189–210, 1938.

Werra[9], quoted by Staehler, clamped the renal artery of dogs for 1 hour. A plain x-ray taken from 3 to 6 days later showed a few areas of calcification in the kidney. X-rays taken in same dogs 7 to 8 days following this showed that calcification had nearly disappeared.

When Marshall and Crane[10] (1923) ligated the renal artery in experimental animals for a few minutes, the urine showed the presence of albumin and no other changes. After the clamp was applied 25 minutes the urine contained a normal or increased amount of water, bicarbonates, and chlorides, but a decreased amount of urea, phosphates, sulphates, ammonia, and creatinin. They explained this effect as due to injury of the tubular epithelium by the ischemia.

Vein. Litten[2] and Harrington[11] (1921) both ligated the renal vein and observed that the kidney became swollen 2 to 3 times normal size and doubled its original weight. Both described dilatation of capsular veins and the suprarenal, spermatic, and lumbar veins. The kidney had a dark purple color, and small hemorrhages appeared in cortex and in tubules of the pyramids. Often hemorrhage occurred under the true capsule and, very rarely, a massive hemorrhage split open the organ. There was necrosis of the renal epithelium and progressive atrophy of all the renal tissue. Renal function was lost and the kidney gradually contracted so that after about 2 to 3 weeks it had reached its normal size. Further contraction continued until the kidney was but a fraction of its normal size.

Rowntree et al.[12] (1913) applied small sections of an ordinary gum rubber catheter of appropriate size about the renal vein or the vena cava in dogs. The degree of constriction was varied from slight to complete. In the incomplete obstruction the urine constantly showed albumin, red blood cells, white blood cells, and casts in varying amounts, and the renal function remained good. In 2 instances where there was complete occlusion of the renal vein, the animals appeared to be in good health. They had good renal function and secreted practically normal urine. This affords evidence of the importance of gradual obstruction to the venous return from the kidneys in allowing time for an efficient collateral circulation to be formed.

Harrington[11] has shown that ligation of a main branch of the renal vein in dogs is not followed by atrophy of the renal parenchyma.

CLINICAL OBSERVATIONS

The literature may be divided into 2 large groups: 1) reported on the basis of clinical and autopsy findings; and 2) based on the clinical findings plus urological examination.

Group 1. Cases reported on basis of clinical and autopsy findings. Traube[13]

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[9] Werra: Quoted by Staehler[8].

[10] Marshall, E. K. and Crane, M. M.: The influence of temporary closure of the renal artery on the amount and composition of the urine. Am. J. Physiol., 64: 387–403, 1923.

[11] Harrington, S. W.: The effect on the kidney of various surgical procedures on the blood supply, capsule and on the ureters. Arch. Surg., 2: 547–592, 1921.

[12] Rowntree, L. G., Fitz, R. and G[illegible] imental chronic passive congestion on renal function. [illegible]

[13] Traube, L.: Uber den Zusammenh[illegible] ---, page 77, Berlin: A, Hirschwald, 1856.

(1856) is credited with making the first diagnosis of renal infarction, clinically. His patient was an 18 year old boy with rheumatic heart disease and aortic insufficiency. The patient was awakened from sleep with severe pain in right renal region, radiating to the right thigh. The pain was steady and was aggravated by percussion in the kidney area and by coughing and moving. The pain was severe for 2 days and then decreased in severity, but the kidney region was very sensitive to percussion. Urine secretion became scanty, dark red color, and contained no albumin. The patient died 9 days after the original onset of pain. At autopsy both kidneys showed many small, depressed, old infarcts, and the right kidney showed a recent infarct occupying the middle one-third. This infarct was the only one which stood up above the surface of the kidney.

Weber[14] (1864) made the diagnosis in a 26 year old woman with rheumatic heart disease who had sudden onset of severe pain in her right lumbar region, accompanied by vomiting, diarrhea, and collapse. There was marked tenderness in the right lumbar region. The pain diminished in the right flank after 2 days, but a few days later she had a similar severe pain in the left lumbar region. This was followed by anuria and death in 2 weeks. Autopsy showed mitral stenosis and large recent infarcts in both kidneys.

Bartel's[15] (1870) patient was an 8 year old boy, who, following a tracheotomy for laryngeal diphtheria, had sudden pain in the left flank and, 2 days later, paralysis of the left thigh. Autopsy showed a large infarct in the left kidney and thrombi in the renal artery and its branches.

Juhel-Renoy[16] (1886) did not make a clinical diagnosis. The patient was a 16 year old girl recovering from scarlet fever who had pain in both lumbar regions, anuria, and died 5 days later. Autopsy showed both kidneys necrotic and multiple thrombi in the renal arteries and veins. No heart or aortic lesions were present.

Von Jurgensen's[17] (1889) patient was a 27 year old woman with mitral-valvular lesion who had 3 attacks of severe pain in the right kidney region, accompanied by vomiting and prostration. The urine contained albumin 3 plus, but no red blood cells. The patient died after third attack. Autopsy showed endocarditis and mitral lesion. The right kidney was fully necrotic and about one-fourth normal size.

Von Leube[18] (1891) made diagnosis of renal infarction in a 17 year old boy with aortic insufficiency. He had an attack of pain in both kidney regions. The urine, which had been normal previously, showed albumin and red blood cells following the attacks of pain. The patient recovered and diagnosis was not confirmed.

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[14] Weber, H.: Kidneys with so-called fibrinous deposits from embolism of the renal arteries. Med. Times and Gaz. (London), 2: 663–664, 1864.

[15] Bartels: Quoted by J. Cohnheim in Untersuchung uber die embolischen Processe, pp. 76–78, Berlin 1872, A. Hirschwald.

[16] Juhel-Renoy, Ed.: De l'anurie precoce scarlatineuse. Arch. gen. d. Med. 7° Ser., T. 17: 385–410, 1886.

[17] Von Jurgensen, T.: Erkrankungen der Kreislaufsorgane. Endocarditis. Vol. 1, No. 15; 105–110. H. Nothnagel's Specielle Pathologie und Therapie, Wein: A. Holder, 1903.

[18] Von Leube, W.: Specielle Diagnose der Inneren Krankheiten. 3rd edition, page 325, Leipzig: F. C. W. Vogel, 1891.

Schmidt[19] (1901–1902) reported 3 cases: The first was a 40 year old man with mitral insufficiency and signs of congestive heart failure during the previous 4 years. He had a sudden onset of pain in the right lumbar region. The urine did not show albumin or red blood cells. Autopsy revealed a mitral stenosis and a massive recent infarct of the right kidney. The second case, a 21 year old girl with acute rheumatic fever and signs of mitral stenosis, was bedridden with congestive failure. She had sudden pain, starting in the right upper quadrant, referred into right flank, and accompanied by nausea, vomiting, and hiccough. The pain was steady and was increased by deep breathing. There was marked tenderness in the right flank. Urine volume was markedly diminished, showed albumin 3 plus, and many red blood cells. She had similar pain in the left flank about 10 days later, became anuric, and died 9 days after this. Autopsy showed many large recent infarcts in both kidneys. The third case, a 45 year old man with a double mitral lesion, was seized suddenly with severe pain in the right lumbar region which subsided after 4 days. Two days later he had severe pain in the left lumbar region and a right hemiplegia. He became anuric and died of uremia. Autopsy showed infarcts of both kidneys and of the brain.

Chedevergne[20] (1902) had a 22 year old man with aortic and mitral disease admitted with dyspnea and arrhythmia. The patient had sudden pain in the popliteal region followed by gangrene of the right leg. Urine showed albumin 3 plus and no casts. Signs of sepsis developed, and the patient died after a few days. Autopsy showed mitral stenosis. Both kidneys contained several old infarcts and a recent infarct the size of an olive in the left kidney.

Achard and Grenet[21] (1903) diagnosed left renal infarction in a 35 year old man with aortic insufficiency who was awakened with violent pain in the left lumbar region. There was marked tenderness in the flank. A Luys separator showed that the left kidney secreted much less urine than the right. Autopsy revealed aortic insufficiency. The left kidney was almost entirely infarcted. A large branch of renal artery was thrombosed.

Bernard and Solomon[22] (1903) reported a woman with mitral insufficiency who died suddenly after an attack of dyspnea. Autopsy showed the left kidney to contain several small, old infarcts. The right kidney was totally infarcted. The renal artery contained a thrombus.

Riebold[23] (1905) diagnosed infarction in a 29 year old woman with cardiac decompensation and mitral lesions who had sudden onset of pain in left lumbar region. The urine was negative. Oliguria developed. At autopsy the left kidney showed a large recent infarct in the upper pole and several smaller ones in the lower pole.

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[19] Schmidt, R.: Zur klinischen Diagnostik des Niereninfarctes und renal bedingter Kolikanfalle. [illegible]
————: Zu [illegible] nd renal bedingter Kolikanfalle. Wien. kl [illegible]
————: Zu [illegible] Wchnschr., 15: 643–648, 1902.

[20] Chedeverg [illegible] Poitou medicin, Poitiers, 17: 185–187, 1902.

[21] Achard, C. and Grenet, H.: Separation des urines dans un cas d'infarctus volumineux de l'un des reins. Bull. et mem. Soc. med. d. hop. de Par., 20: 342–345, 1903.

[22] Bernard, L. and [illegible] al du rein par embolie de l'artere renale chez une asystolique. [illegible] Par. 77: 690–693, 1903.

[23] Riebold, Geo.: B [illegible] der Milz- und Niereninfarkte, und zur Kasuistik von Herdlasionen im Thalamus Opticus. Deutsches Arch f. klin. Med., 84: 498–517, 1905.

Halperin[24] (1908) describes a 44 year old man, a severe hypertensive who, 1½ years before, had had his lower left leg amputated because of progressive gangrene. He re-entered the hospital complaining of continuous pain in left upper quadrant of 2 weeks' duration, accompained by vomiting. While in the hospital he had 2 attacks of pain, each lasting 4 days, occurring first in the left lumbar region and then in the right. Each attack was accompanied by severe vomiting and headache, and slight fever. Leukocytosis was 28,000. Urine, after the second attack, showed albumin 2 plus, a few red blood cells and casts, and some hemoglobin. Sometime later he had another severe attack of pain in left flank, followed by anuria. The left kidney was exposed. It was incised through the convex border to the pelvis. The cut surface was pale and almost bloodless. The patient died on the second postoperative day of uremia. At autopsy two-thirds of the left kidney was infarcted. The left renal artery was obliterated by an adherent thrombus. The right kidney was about one-half the normal size and the upper pole was infarcted. The renal vessels showed pronounced arteriosclerotic changes. The heart showed no endocarditis or valvular lesions.

Rey[25] (1910–1911) reported 4 cases: 1) The patient was admitted because of sudden onset of pain in the right side of the abdomen. Examination revealed cardiac irregularity and dilatation. Urine showed albumin 3 plus. Death occurred 15 days later without any change in signs. Autopsy revealed mitral lesions and total infarction of right kidney. The right renal artery was filled with an adherent thrombus. The left kidney was enlarged and showed scattered small abscesses in cortex. 2) The patient developed sudden pain in right lumbar region, radiating to groin and thigh. The urine showed red blood cells and diminished volume. Fifteen days later, the patient had similar pain in the left lumbar region radiating to the groin and thigh. Anuria followed, and death 15 days later. Autopsy showed infarction of right kidney, probably due to embolus. 3) A patient with clinical diagnosis of chronic Brights disease, cardiac hypertrophy, uremia, died 1 month after admission to the hospital. Autopsy showed total infarction of left kidney and a thrombus filling left renal artery. 4) A 46 year old patient with mitral stenosis was admitted because of palpitation and tachycardia. While in hospital she suddenly had severe pain in the right lumbar region, radiating to right thigh. The urine contained red blood cells and albumin 3 plus. Previous to this, the urine had been negative.

Pic and Bonnamour[26] (1913) made a diagnosis of renal infarction in a 69 year old woman with left hemiplegia and aortic insufficiency, who had a sudden attack of pain in left lumbar region and left upper quadrant. The pain was steady and did not radiate. The urine output fell to 50 cc in a day and the albumin was 3 plus. The temperature rose gradually to 101.½°. The pain gradually diminished and patient died 2 days later. Autopsy showed arteriosclerosis of the aorta and a subtotal infarct of left kidney, with a thrombus in a branch of the renal artery.

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[24] Halperin, Geo.: Clinical manifestations of hemorrhagic renal infarct. Arch. Int. Med., 1: 320–328, 1908.

[25] Rey, F.: Contribution a l'etude clinique des infarctus renaux. pages 1 to 67, A. Maloine, Lyon 1911.

[26] Pic, A. and Bonnamour, S.: Infarctus subtotal du rein gauche par thrombose de l' artere renal. Lyon méd., 120: 1306–1309, 1913.

Von Jagic[27] (1915) reports a case of a 39 year old woman with rheumatic heart disease who had sudden onset of pain in left side of abdomen 3 weeks before admission. On admission there was tenderness in left upper quadrant. The abdomen was rather distended. The temperature was 102°. The urine output was 500 cc and showed albumin 3 plus, no red blood cells, and specific gravity of 1.023. The pain and temperature subsided after 3 or 4 days. Six days later she had similar pain in the right upper quadrant. The right kidney was palpable and tender. Anuria developed and the patient died 12 days later. Autopsy showed mural thrombi in the left auricle and ventricle, and mitral stenosis. Both kidneys showed massive infarction, and renal arteries contained emboli.

Summary: In the above cases, the diagnosis was suspected from the sudden onset of pain in the kidney area in cardiac patients. The pain was steady and radiated to the thigh in but 3 of the 20 cases. The pain was severe for about 2 days and was accompanied by vomiting in about half the cases. The urine contained albumin, and sediment showed red cells in half the cases. The urine was reported to be negative in only 2 instances. Death occurred from anuria and cardiac failure in all cases except the one reported by Von Leube[18]. In this case the diagnosis was not confirmed pathologically. In most of the cases there were many old, small infarcts in both the kidneys, in addition to the recent infarction. No cardiac lesion was found in the 3 cases reported by Bartel[15], Juhel-Renoy[16], and Halperin[24]. Bartel's case followed operation and was associated with embolism of the left femoral artery. Juhel-Renoy made no diagnosis clinically, but found thrombosis of the intrarenal arteries and veins of both kidneys in a girl dying of anuria, following scarlet fever. Halperin's case was hypertensive with marked arteriosclerosis of the renal vessels.

Group 2. Cases based on clinical findings plus urological examination. To save space these have been tabulated (table 1).

Summary: Seventy collected cases comprise 47 arterial, 20 venous, and 3 traumatic infarctions. In the arterial cases pain began suddenly, was situated in the flank or upper abdomen, and persisted for 2 to 4 days. It resembled renal colic in 3 instances and radiated to the thigh in 2. There was gross hematuria in 6 cases. (Duvergey and Dax[30], Staehler[8], and Wolffe[52] each reported 1 case, and Richard[51] reported 3 cases.) Disease of the heart or blood vessels was present in 34 of 47 cases. Nathan[35] operated upon 2 cases with perirenal subcapsular hematoma. The only lesion present in the kidneys was anemic infarct. Metzler[32], who operated for suspected tumor of the kidney, found subcapsular hemorrhage overlying an infarct of the upper pole. Hardeman[56] found massive, bilateral, perirenal hemorrhage and renal infarction in a patient who had peri-

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[27] Von Jagic, N.: Zur Symptomatologie der Niereninfarkte. Wien. med. Wchnschr., 65: 290–293, 1915.

TABLE 1

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Aschner[28] 1922	31 year female	Pain localized left flank. Three days duration. Vomiting. Heart enlarged, pre-systolic murmur at apex. Tenderness and rigidity left upper quadrant and left flank. Temperature 101.8° 20,000 white blood count. 82 per cent neutrophiles. Urine showed albumin 1+ occasional white blood cells and casts.	Plain film negative for stone. Cystoscopy: Normal bladder and ureter. Indigo carmine* delayed secretion both sides. Operation showed 2 recent infarcts in the left kidney.	None
Aschner (No. 2)	44 year female	Auricular fibrillation. One day's duration of abdominal pain localized in right upper quadrant. Marked tenderness right upper quadrant and right flank. Acute pain subsided after 2 days. White blood count: 24,000. Neutrophiles: 91 per cent. Urine: albumin 3+, many red blood cells, and a few casts.	Total phenolsulphonphthalein 35 per cent in 2 hours. Cystoscopy showed normal bladder and ureters. Good function on both sides.	None
Bull[29] 1923	35 year female	Sudden onset of pain in left upper quadrant and left flank day before admission, accompanied by vomiting and abdominal distension. Heart showed pre-systolic murmur at apex and irregular rhythm. Marked tenderness over left kidney area. 11,200 white blood count. Urine showed albumin 1+.	Cystoscopy: Normal bladder and ureters. Blue test* excellent on right and no secretion left side. Plain film negative for stone. Left nephrectomy showed large infarct middle third of kidney. Patient died suddenly on sixteenth postoperative day.	Mitral stenosis. Mural thrombus in left auricle. Several small infarcts in spleen and right kidney.
Duvergey and Dax[30] 1925	43 year female	Developed acute pain 10 days before admisson in right lumbar region. Pain persisted and 5 days later hematuria occurred. Examination revealed rheumatic heart disease with mitral stenosis. Tenderness and spasm in right lumbar region. Urine was bloody.	Cystoscopy: Bladder normal. Bloody urine coming from right ureter. Right nephrectomy 4 days after admission. Kidney normal size and soft. On section middle and lower one-third were dull and markings were lost. A pale clot was found in renal artery. Miscroscopic examination showed few areas in cortex of nodular inflammation resembling focal tuberculosis.	None
Makai[31] 1926	13 year male	Patient ill for 2 weeks with headache, fever, and pain in right lower quadrant. Examination revealed heart normal, pulse regular, and temperature 103.6°. Spasm, tenderness, and an indefinite mass noted in ileocecal region. 78,000 white blood count. Urine: Albumin 1+, few red blood cells, and few white blood cells.	Operation revealed normal appendix and retroperitoneal mass behind right colon. Mass was congenital fused kidney with both pelves faced medially. On posterior surface of lower kidney was a yellowish area size of 50 cent piece. Drain was placed and wound closed. Postoperative course good until seventh postoperative day when oliguria developed and red blood cells appeared in urine. Patient died on twelfth postoperative day.	Verrucous endocarditis of mitral valve. Red infarct in spleen. White infarct and nephritis in fused kidney.

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* Indigo carmine.

[28] Aschner, P. W.: The clinical importance of aseptic infarction of the kidney. Am. J. M. Sc., 164: 386–389, 1922.

[29] Bull, P.: Diagnostizierte Embolie der linken Arteria renalis, Nephrectomie, Mors subitanea sechzehn Tage nach der Operation. Ztschr. f. urolog. Chir. u. Gynak., 14: 201–214, 1923.

[30] Duvergey, J. and Dax, L.: Necrose du rein droit par embolie arterielle. Nephrectomie. Guerison. J. d'urol., 20: 151–154, 1925.

[31] Makai, E.: Appendicitisfehldiagnose beim Infarkt einer einseitigen Verschmelzungsniere (Langniere). Zentralbl. f. Chir., 53: 2977–2979, 1926.

TABLE 1—*Continued*

AUTHOR	*CASE*	*CLINICAL BRIEF*	*UROLOGICAL FINDINGS*	*AUTOPSY*
Metzler[32] 1928	45 year female	Two days before admission, sudden onset of pain in right flank, accompanied by vomiting Examination showed temperature 99 5° systolic murmur at apex, marked tenderness in right flank Pain subsided after 2 days Urine showed a trace of albumin	Cystoscopy Bladder and ureters normal Indigo carmine appeared in 10 minutes with good color on left side, none secreted from right side Right retrograde pyelogram showed normal ureter but pelvis did not fill completely Operation for suspected tumor Kidney normal size with blood clots beneath the capsule Upper half of kidney was grayish white infarct	None
Metzler (No 2)	34 year female	Known cardiac who had sudden attack of pain in right upper quadrant 2 days before admission Temperature 99°, pulse irregular Spasm and tenderness in right side of abdomen An indefinite mass could be felt above cecum	Laparotomy revealed normal appendix and gallbladder Right kidney exposed, large infarct present in the upper pole	None
McKenna[33] 1928	29 year male	Patient complained of aching pain in right flank and dysuria Examination revealed that he was acutely ill Temperature 99° Tenderness and rigidity in right lumbar region Albumin 1+ 13 000 white blood count 81 per cent neutrophiles	Cystoscopy revealed impermeable urethral stricture Six hours after cystoscopy he had chill and fever to 104 8° He died of sepsis 10 days later	Acute bacterial endocarditis of aortic valve Right kidney totally infarcted Right renal artery occluded with thrombus Multiple small infarcts in spleen and left kidney
Wosnessensky[34] 1928	52 year female	Patient had sudden onset of pain in epigastrium along with vomiting abdominal distension, and anuria 2 days before admission Heart sounds regular and systolic murmur at apex Marked tenderness in both flanks and in right upper quadrant	Catheter obtained small amount of bloody urine Plain film negative for stone Laparotomy revealed nothing of importance Patient died of uremia 11 days after admission	Mitral *stenosis* Mural thrombus in left auricle Emboli occluded both renal arteries Total infarction of both kidneys
Nathan[35] 1932		Author discussed 2 cases of perirenal hematoma	At operation an anemic infarct was found in involved kidney Author believed infarct was caused by infected embolus and hemorrhage due to erosion of nearby vessels	
Weiss[36] 1932	55 year male	Six weeks before admission, right hemiplegia Three days before admission sudden attack of pain in left flank Pain steady and radiated to left thigh Heart enlarged Marked tenderness in left upper quadrant and left flank Pain gradually went away during the next 2 days On eighth hospital day, severe pain in left upper quadrant X ray of chest showed opacity of left costopleural sinus	Cystoscopy on nineteenth hospital day showed no dye excretion on left side Intravenous pyelography showed good function on right side but no function on left side Left retrograde pyelogram showed normal calyces, pelvis, and ureter Intravenous pyelography on thirty third hospital day showed no function on left side and good function on right side	

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er Arteriae renalis, kombiniert m

Niereninfarkt Zentralbl f Chir, 59: 496–497, 1932

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Wildbolz[37] 1932	52 year male	Repeated attacks of severe left renal colic during a 5 year period. On admission, symptoms of cardiac failure, pain in left flank, and low grade fever.	Repeated cystoscopies, excretory and retrograde pyelography, made during 5-year period had all failed to reveal cause of symptoms. Left nephrectomy; large wedge-shaped infarct occupied middle third of kidney.	
Barney and Mintz[38] 1933	29 year female	Admitted with lobar pneumonia which cleared by lysis after 1 week in hospital. About 2 weeks later she had recurrence of pain in chest, fever, and signs of pneumonia. Ten days following this, sudden, severe pain in right loin. Pain persisted and patient vomited once. Marked tenderness in right upper quadrant and right flank.	Laparotomy revealed nothing abnormal except rather large right kidney. Patient died on the ninth postoperative day.	Ulcerative endocarditis of aortic valve. Right kidney was completely infarcted. Left kidney was normal.
Barney and Mintz (No. 2)	35 year female	Admitted with congestive heart failure. She complained of no pain; no tenderness in flanks. Edema and gangrene of legs developed and patient died 2 days after admission.		Right kidney showed infarct of about one-quarter of its tissue. Left kidney was nearly all infarcted.
Barney and Mintz (No. 3)	65 year male	Entered hospital because of anasarca and uremia. On seventeenth hospital day, pain in right lower quadrant of abdomen. Pain constant, not relieved by morphine. Urine negative. Death on twenty-second hospital day.		Total infarction of right kidney. Several small infarcts in left kidney.
Barney and Mintz (No. 4)	No age given male	Three days before admission he fell off a moving car, injuring head and back. On examination, in shock, pulseless; dullness in right flank. Catheter obtained 60 cc bloody urine. Death 8 days after admission.		Large infarct in right kidney. Left renal vessels were thrombosed.
Adler-Racz[39] 1933	40 year female	Severe cardiac, for 3 years known to have stones and infection in right kidney. Three weeks before admission, she had sudden attack of pain in left flank with suppression of urine. Pain was severe for a few days and patient voided small amounts of bloody urine each day.	Cystoscopy revealed bladder mucosa rather red. No obstruction in left ureter and no dye secreted from left kidney. Left retrograde pyelogram showed kidney rather small and the calyces somewhat flattened. Patient died 2 months after admission.	Mitral stenosis and mural thrombus in left auricle. Left kidney almost fully infarcted. Right calculous pyonephrosis and tuberculosis of pelvis and ureter.
Cohn[40] 1933	23 year female	Persistent left pyelonephritis for about 2 years. Admitted because of recurrent pain in left flank and foul smelling urine Examination negative except for secondary anemia. Urine loaded with white blood cells and bacilli.	Intravenous pyelography: Left pelvis incompletely filled; normal functioning right kidney. Cystoscopy revealed normal bladder and no obstruction in ureters. Urine from left kidney cloudy. Left kidney removed; infarcts in the upper and lower pole. Thrombus present in retropelvic artery.	

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[39] Adler-Racz, A.: Ein Fall von Embolie der Nierenarterie. Ztschr. f. Urol., 27: 40–44, 1933.

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Folsom and Alexander[41] 1934	54 year female	Patient known to have auricular fibrillation for a period of 12 years For past 5 years she had repeated attacks of asthma and congestive heart failure Five years before admission acute attack of pain in right upper quadrant fairly normal gallbladder and appendix removed Five days before admission patient developed a cold followed by an asthma attack Sudden onset of severe pain in right upper quadrant 2 days before admission She became uremic Examination showed irregular heart beat and tenderness in right side of abdomen, both in front and back Patient died of uremia 4 days after admission	Plain film negative for stone Cystoscopy Normal bladder, catheters met no obstruction in either ureter Right retrograde pyelogram showed bizarre distortion of the pelvis and calyces Two days later cystoscopy was repeated and indigo carmine showed practically no function from either kidney Bilateral retrograde pyelograms showed same distortion on right side left kidney small and hypoplastic	Mitral stenosis Mural thrombus in left auricle Right kidney showed a large old infarct, and many large recent infarcts Left kidney showed fibrotic atrophy
Ehrstrom[42] 1934	Age and sex not stated	Author made a diagnosis of renal infarction in patient with symptoms and signs of endocarditis and sudden attack of colicky pain in left flank	Intravenous pyelography Normal functioning right kidney and no function of left kidney Bilateral retrograde pyelograms showed normal renal pelvis both sides *Intravenous pyelography* on the twenty third hospital day showed some function on left side but much poorer than right side Intravenous pyelography on fortieth hospital day showed good function on both sides	
Desjacques and Boijeau[43] 1936	52 year male	Patient awakened from sleep with severe pain in both lumbar regions and in epigastrium Pain was persistent and he vomited several times Examination blood pressure 190/150 and marked tenderness in epigastrium and both flanks	Laparotomy revealed no definite disease Patient died suddenly on eighth postoperative day	Syphilitic aortitis with rupture in transverse aorta Left kidney normal Right kidney showed a large infarct of upper pole
Westerborn[3] 1937	49 year male	Patient had had several attacks of cerebral embolism and embolism of right femoral artery While convalescing from left hemiplegia sudden attack of pain in right flank Pain was constant and did not radiate Temperature 102 2 Urine showed albumin 1+	Intravenous pyelography showed no function of right kidney and good function of left Cystoscopy revealed normal bladder and ureters Indigo carmine did *not appear on right side* Right retrograde pyelogram normal Right kidney was exposed and no pulsation could be felt in renal vessels After massaging renal artery, pulse could be felt Cystoscopy 11 days after operation showed indigo carmine secretion from right side, fair color, in 30 minutes Thirty nine days after operation intravenous pyelography showed no function in right kidney and right nephrectomy was done Patient re-admitted 6 months after complaining of abdominal pain and anuria Left kidney exposed and thrombus removed from renal artery Patient died 2 days after operation	Mitral stenosis Mural thrombus in left auricle Left kidney was to*tally* infarcted and there were thrombi in all branches of renal artery

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197–198, 1934

[42] Klinik des Niereninfarkts und der Nierenvenenthrombose Reviewed in Ztschr f urolog chir u Gynak , 40. 119, 1934

[43] Desjacques, J and Boijeau, A Les Gros Infarctus du Rein Lyon Chir , 33: 645–674, 1936

TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Stachler[8] 1938	69 year female	Patient was admitted to hospital with diagnosis of nephritis. Heart enlarged, edema of both legs, and in left upper quadrant was an indefinite mass, presumably kidney. Urine showed albumin 3+, and many red blood cells.	Intravenous pyelography showed no function of left kidney. Left retrograde pyelogram revealed that pelvis did not fill with medium. Left nephrectomy was done. Kidney dark red with yellow areas on surface. Renal artery and vein were filled with thrombi.	
Stachler (No. 2)	36 year male	Three days before admission, sudden onset of pain in right flank and severe pain in right leg. On admission right lower leg was cold and discolored with ecchymosis. Right leg was amputated.	Intravenous pyelography 8 days after amputation showed good function of left kidney and no function of right kidney. Intravenous pyelography 4 weeks later showed good function both sides.	
Stachler (No. 3)	40 year male	Patient had had 2 attacks of severe and persistent hematuria. On admission heart was normal and abdomen was negative.	Indigo carmine showed no secretion from right side and good color from left side. Right kidney was exposed and a single circumscribed lesion was found in cortex. Lesion was excised and microscopic examination showed necrosis in center with hemorrhages and cell infiltration in periphery.	
Pirn[44] 1939	22 year female	Fever and sore throat 2 weeks before admission. She noticed dysuria about a week before admission. Chill and severe pain in left flank, radiating to left groin, night before admission. Examination showed heart and lungs negative, temperature 102.6°. A tender mass could be felt in left flank.	Cystoscopy showed no obstruction in left ureter. Urine showed trace of albumin and many white and red blood cells. Catheter left indwelling in left ureter. About an hour after cystoscopy patient had typical signs of pulmonary embolism. Temperature became septic type accompanied by chills and left flank pain. Left kidney was removed; necrotic area in lower pole. Center of the lesion contained purulent material. Secondary venous thrombosis.	
Foley[45] 1940	55 year female	Mitral disease and auricular fibrillation. Admitted to hospital soon after sudden onset of pain in left flank. Exquisite tenderness in left flank and transient hematuria and albuminuria. Pain gradually subsided, and further course was uneventful.	Intravenous pyelography showed normal functioning right kidney and no function of left kidney. Cystoscopy showed normal excretion of indigo carmine on right, and none from left kidney. Left retrograde pyelogram showed general magnification of the pelvis and calyces, but no obstruction or actual dilatation of pelvis. Intravenous and retrograde pyelography were repeated 1 and 2 months later, and on both occasions showed normal right and a totally nonfunctioning left kidney. Retrograde pyelograms showed marked decrease in size of left renal pelvis. A retrograde pyelogram made 1½ years later showed that changes had progressed to near disappearance of kidney exactly like picture seen in autonephrectomy.	

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AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Sheppard[46] 1939	24 year male	Patient awakened from sleep 3 days before admission with severe pain in left loin Pain constant and accompanied by vomiting No urinary complaints Heart and lungs normal, marked tenderness in the left hypochondrium and left flank Urine negative Pain persisted and patient had temperature up to 100°-101°	Plain film negative for stone Intravenous pyelogram taken 5 days after admission showed normal functioning right kidney but no function of left kidney On eighth hospital day, left kidney exposed Renal pedicle did not pulsate and vessels were matted together Both renal artery and vein contained thrombi	
Hoxie and Coggin[47] 1940	38 year female	Patient with rheumatic heart disease who had sudden onset of pain in both lumbar regions 3 days before admission Pain radiated around flanks into upper abdomen Pain accompanied by anuria, nausea and vomiting Heart enlarged and rhythm irregular Abdomen tympanitic and tender in flanks and epigastrium About 5 cc bloody urine obtained by catheter Spectroscopic examination showed presence of hemoglobin Patient died of uremia 10 days after admission		Mitral stenosis Mural thrombus in left auricle Both kidneys infarcted Renal arteries contained loose antemortem clots
Hosel[48] 1939	74 year female	Sudden onset of pain in right upper abdomen and right kidney region 3 days before admission Pain steady and persisted up to admission and there were no urinary complaints Heart enlarged with completely irregular rhythm Spasm and tenderness in right flank Urine showed albumin a trace, and an occasional red and white blood cell	Cystoscopy Bladder and ureters normal Indigo carmine appeared readily with good color from left side and no dye appeared from right side Right retrograde pyelogram revealed normal calyces pelvis and ureter Right nephrectomy, kidney soft, markings blurred Large branch of renal artery contained thrombus	
Vogelsang[49] 1940	19 year female	Gradual onset of pain in right side of abdomen and right flank Pain persisted and patient admitted to hospital same day Heart and lungs were normal Some tenderness in right upper quadrant and right flank Urine showed albumin 4+ and few red and white cells	Cystoscopy showed cloudy urine from right ureter Catheter easily passed up right ureter and was left indwelling Right retrograde pyelogram showed normal calyces pelvis, and ureter Patient was given a transfusion of whole blood Following this she had cyanosis, dyspnea, and signs of shock and died within 48 hours	Two pyramidal shaped hemorrhagic infarcts in right kidney
Emmett and Dreyfuss[50] 1941	50 year female	Cholecystectomy and appendectomy on third postoperative day auricular fibrillation developed Digitalis given for 2 days On the fourteenth postoperative day complained of severe pain in right kidney region and became nauseated and vomited Urine showed 10 white blood cells and an occasional granular cast	Cystoscopy showed practically no secretion of urine from right kidney Cystoscopy was repeated several times during the next 3 weeks and no urine was obtained from right kidney Right kidney was exposed, it was of good size and about four-fifths of it a dull yellow color Microscopic study showed almost complete necrosis except for small area near lower ople	

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Richard[51] 1942	58 year female	Cholecystectomy; convalescence satisfactory until fifth postoperative day when severe pain developed in right lower side of abdomen. Meteorism and anuria developed. Patient died of uremia on the seventh postoperative day.		Wound normal. No hemorrhage in peritoneal cavity. Fused kidney in true pelvis. Middle third of right half of kidney had a yellow color and was surrounded by red border. Thrombus occluded lumen of principal artery to this part of kidney. Heart normal. Atheromatous lesions in aorta.
Richard (No. 2)	14 year male	Appendectomy; normal postoperative course until sixth day. Sudden attack of pain in right upper abdomen, radiating into back. Marked tenderness over right kidney area. Urine showed albumin 1+ and many red blood cells. The pain had nearly disappeared by the tenth postoperative day.	Intravenous pyelography revealed no function of right kidney and normal function of left. Right retrograde pyelogram showed normal renal pelvis. Three months after discharge from hospital urine was normal. Intravenous pyelography showed good function on both sides.	
Richard (No. 3)	21 year female	Appendectomy; uncomplicated postoperative course until fifth day. Pain in right upper quadrant, radiating around into back. Urine on first day of pain was normal and later showed red blood cells. Pain and tenderness in right kidney gradually went away.	Intravenous pyelography 8 weeks later gave normal findings. Urine was negative.	
Richard (No. 4)	56 year male	Patient was up and about on seventh day following appendectomy. Three days later, sudden pain in right flank, and hematuria.	Intravenous pyelography showed poor function on right side on 20 minute film; normal function of left kidney. Eight days later, symptom free. Right retrograde pyelogram showed normal pelvis.	
Richard (No. 5)	42 year female	Supravaginal hysterectomy. On seventh postoperative day, attack of pain in right flank and hematuria. Hematuria was still present after 3 weeks.	Cystoscopy showed bloody urine coming from right ureter. No obstruction in right ureter. Right retrograde pyelogram showed normal pelvis.	
Richard (No. 6)	53 year male	Bilateral inguinal hernia repair. On the seventh postoperative day, sudden onset of pain in left flank, abdominal distension, and hematuria. Marked tenderness in left renal area.	Cystoscopy showed renal pelvis unchanged.	

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Wolffe[52] 1941	59 year male	Sudden onset of pain in right upper abdomen and right flank Past history of gaseous indigestion Examination showed abdomen distended, entire right side tender and rigid Urine showed albumin 1+ and many red blood cells Cholecystectomy Patient died of shock on second postoperative day		Marked arteriosclerosis of aorta and both renal arteries Lower pole of right kidney infarcted and a thrombus in lower branch of renal artery
Wolffe (No 2)	54 year male	Pain in left flank and nausea and vomiting Temperature slightly elevated Urine showed red blood cells	Intravenous pyelography showed incomplete filling of calyces of left kidney and normal functioning right kidney Left retrograde pyelogram negative Intravenous pyelography 6 months and another 1 year later showed only a remnant of filling defect of the calyces of left kidney	
Wolffe (No 3)	58 year male	Sharp pain below left nipple Pain radiated to left side of abdomen Marked arteriosclerosis and blood pressure of 190/100 A few hours after admission pain shifted to left kidney region White blood count 19,700 Urine contained many red blood cells During next few days temperature varied from 99° to 100 2°	Intravenous pyelography revealed absence of stone and a filling defect of middle and lower calyces of left kidney	
Wolffe (No 4)	57 year female	Myocardial insufficiency and, on admission complained of sharp pain in left kidney area Pain radiated to left lower quadrant, and there was dysuria and hematuria	Intravenous pyelography showed left major and minor calyces were rather narrow and irregular, suggesting chronic pyelonephritis. Left retrograde pyelogram showed some irregularity of the lower calyces	
Oppenheimer[53] 1942	26 year female	Rheumatic heart disease Four days before admission sudden onset of colicky pain in right flank Blood pressure on admission was 118/60 and rose to 170/100 2 weeks later Patient died of congestive heart failure 4 weeks after admission	Intravenous pyelography showed normal function of left kidney and absence of function of right kidney Cystoscopy revealed normal bladder and ureters Indigo carmine appeared promptly from left side and none appeared from right side Retrograde pyelogram negative	
Prinzmetal[54] 1942	53 year female	Rheumatic heart disease with auricular fibrillation and on admission complained of dyspnea and epigastric pain Urine showed albumin 2+ and many white and red blood cells Normal cardiac rhythm restored by the use of quinidine Blood pressure 130/100 Progressive oliguria developed and blood pressure rose to 190/100 Patient died of uremia on twenty first hospital day		Ulcerative athermatous lesions of aorta thrombus occluded orifices of both renal arteries

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[53] Oppenheimer, G C Aseptic infarction of the kidney J Mt Sinai Hosp , 8: 1220–1224, 1942

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Sole[55] 1943	43 year male	Left calculous pyonephrosis.	Left kidney exposed; when it was split to expose large stone, there was practically no bleeding. Stone removed. Biopsy of the renal tissue showed necrosis of tubular epithelium. Intravenous pyelogram taken 1½ and 4 months postoperatively showed no function of left kidney.	
Hardeman[56] 1944	35 year male	During 3 months before admission, recurrent acute arthritis of shoulders, legs, and feet. On admission patient acutely ill; spiking septic temperature. On thirteenth hospital day, pain in right side of abdomen, accompanied by signs of shock. Two days later, acute pain in the left kidney area; again, signs of shock. Urinary output remained unchanged. Patient died on thirty-fifth hospital day.		Bilateral massive perirenal hemorrhages with total infarction of both kidneys. Aneurysmic dilatations of interlobular arteries. There were nodular thrombotic changes in arteries of various organs. Diagnosis of periarteritis nodosa was made.
Ben-Asher[57] 1945	43 year female	Mitral stenosis and cardiac insufficiency. Twelve hours before admission, sudden onset of pain in right upper quadrant and right flank. Anuria for 8 hours, followed by hematuria. Irregular heart rhythm and abdominal distention. Marked tenderness over right upper quadrant. Temperature 103.4°. Urine showed albumin 4+ and many red blood cells. Transient hypertension following subsidence of acute symptoms.	Intravenous pyelography showed normal functioning left kidney and no function of right kidney. Right retrograde pyelogram showed normal pelvis and ureter. Intravenous pyelography 1 month later showed normal function both sides.	
Hirshberg and Soll[58] 1942	48 year male	Back injured in a truck accident 3 days before admission. Following accident, pain in left flank and hematuria. On admission, marked tenderness; mass felt in left flank.	Intravenous pyelography showed no function of left kidney. Left nephrectomy 2 days later. Fluid and blood in perinephric tissues. Blood clots in hylus region. Kidney was a dark red color and had a mottled surface.	
Rexford and Connolly[59] 1945	27 year male	Patient crushed between a moving crane and side of building. X-rays revealed no fractures. Pain in upper abdomen, chest, and shoulders. Examination of abdomen revealed exquisite tenderness in mid-epigastrium and left upper quadrant. Urine remained clear except that albumin increased to 4+ 2 days after admission.	Intravenous pyelography made on the third hospital day showed no function of left kidney; good function of right kidney. Left retrograde pyelogram showed normal calyces, pelvis, and ureter. On the fifteenth hospital day left nephrectomy. Kidney surrounded by thick, mottled, grey capsule. Section of kidney revealed 3 yellowish gray triangular areas which were recent infarcts. More than 50 per cent of renal tissue destroyed.	

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Cedernark, Lindblom, and Henschen[60] 1941	37 year male	April 1941, complained of severe pain in right flank radiating to right groin Also frequency, chills and vomiting Marked tenderness over right kidney Temperature 102 2° Heart and lungs normal *Urine contained* many red and white blood cells Symptoms improved and patient was discharged 10 days after admission Re-admitted June 26 1941 complaining of steady pain in right flank Tenderness over the right kidney region Urine negative	Intravenous pyelography showed loss of function of right kidney Cystoscopy showed normal bladder ureteral catheter passed an obstruction 10 cm up right ureter Right retrograde py*elogram showed normal pelvis* and ureter Intravenous pyelography 8 days later showed no function of right kidney After re admission intravenous pyelography showed no function in right kidney Aortagraphy showed good filling of left renal artery and intrarenal vessels, but failed to fill right renal artery or any of intrarenal vessels Internal spermatic and lumbar arteries were filled with medium Right *nephrectomy July 17* Kidney was small and hard and on section upper half was infarcted Renal artery contained an organizing thrombus	
Heller[61] 1923	9 day male	Vomiting diarrhea, blood in stools and convulsions Two days after admission, severe hematuria Mass in left hypochondrium was thought to be kidney Vomiting persisted and infant became dehydrated and emaciated *Anuria occurred on* eleventh hospital day and death 4 days later	Plain film showed a very large renal shadow on the left side	Kidneys large and dark red color, and on sections markings were indistinct Renal veins and *inferior* vena cava thrombosed
Aschner[62] 1927	2 month male	Patient had had a cold for 2 weeks and was admitted when there occurred signs of lobular pneumonia Five days after admission a mass could be felt in right lumbar region Mass became progressively larger Urine specific gravity 1 040 and there were a few white blood cells and granular *casts Infant died 2 days* later		Purulent tracheobronchitis and organizing pneumonitis Right kidney 3 times normal size and dark purplish color Right renal vein contained pinkish white thrombus
Grüneberg[63] 1932	3 month male	Severe gastro-enteritis and hematuria Painful tumor about 25 cm long developed in left kidney region	Left kidney removed Patient gradually improved Kidney was about 3 times normal size and showed thrombosis of main renal vein. Renal artery not thrombosed	
Campbell and Matthews[64] 1942	13 day male	Infant well until the fifth day of life when he had fever, vomiting, and blood stained stools Examination revealed a greatly enlarged right kidney Urine showed blood albumin pus and pus casts	Retrograde pyelogram showed right *ureter to be well filled* and pushed slightly toward midline of abdomen Pelvis did not fill with opaque medium Nephrectomy Kidney was dark chocolate color and resembled large blood clot Pelvic vessels were firmly thrombosed	

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[64] Campbell, M F and Matthews, W F Renal thrombosis in infancy J Pediat , 20. 604–615, 1942

TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Campbell and Matthews (No. 2)	29 day male	Patient well until the seventh day of life when he became acutely ill and vomited most of food. Stools blood streaked and he had some fever. About 2 weeks after admission, mass in the right kidney region. Urine showed blood, pus, and albumin.	Right retrograde pyelogram showed satisfactory ureteral filling but pelvis did not fill. After further injection the medium spread through parenchymal substance, but no pelvic outlines were visible. Nephrectomy. Kidney was bluish-black with small abscesses in cortex. Pelvis contained thick bluish pus. Lower pole of kidney was infarcted.	
Fahr[65] 1903	2 year female	Patient admitted with abscess of left groin. Abscess incised and drained. Pymeia developed. Death a week later. She had complete anuria several days before death.		Phlegmon of left groin communicating with abscess beneath broad ligament on left side of pelvis. Left iliac vein, inferior vena cava, and both renal veins were filled with thrombi. Kidneys were enlarged and necrotic. Capsule of right kidney was elevated by hemorrhages.
Derow, SchleSinger, and Savitz[66] 1939	15 year male	Sudden attack of pain in left flank radiating across left side of abdomen. Because of pain and low grade fever, admitted to hospital in May 1935. Many urinalyses showed albumin varying from 1+ to 4+. Blood pressure was normal and kidney function was good. He was discharged with a diagnosis of nephrosis. Patient was well until 4 months later. Patient re-admitted because of severe pain in right side of abdomen radiating to right groin and right flank. Renal function good. Urine showed albumin 1+ to 4+ and occasional white and red blood cells and casts. Two weeks after admission, swelling of the legs and enlargement of the abdomen developed. Final admission to hospital, October 1936. Chills, fever, nausea, vomiting, and diarrhea of 1 day's duration. Urine showed specific gravity 1.020, albumin 2+, 20 white blood cells, and 5 red blood cells, and few granular casts. Patient went into coma and died 2 days later. Death caused by pneumococcal peritonitis.	Intravenous pyelography showed renal pelves to be rather small and the calyces elongated and narrow.	Inferior vena cava and both renal veins were solid cords and contained recanalized thrombi of various ages. Branches of renal veins were patent. No gross intrarenal thrombosis. Kidneys were large; capsules thin and stripped easily. Calyces and pelvis had smooth, normal appearing mucosa. Microscopic examination showed normal glomeruli, slight cloudy swelling of tubular epithelium, some interstitial edema, and occasional collection of round cells.

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TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Aschner[42] 1927	65 year male	Weakness, cough, dyspnea, and abdominal pain Swelling of eyelids and feet and pneumonia in right upper lobe Urine showed albumin 3+, many pus cells and casts Two weeks after admission right kidney became enlarged and tender and temperature rose to 102°	Cystoscopy showed large prostate, trabeculated bladder, dilated ureters and pelves, and large kidneys No excretion of indigo carmine from right side in 30 minutes He was placed on catheter drainage Temperature rose He became stuporous and died 3 days later	Kidneys showed cortical abscesses and pyonephrosis Renal veins contained yellowish thrombi extending from within organ to where they joined chief branch
Aschner (No 2)	42 year male	Furuncle of left temporal region that discharged spontaneously, then healed Nine days later, fever and chills, pleurisy on right side and later an abscess of right fibula Blood culture positive for Staphlococcus albus Urine showed albumin 1+ and oc white blood cell Patient died 5 days after admission		Cortical abscesses of left kidney Renal veins leading from these areas contained grayish red thrombi
Aschner (No 3)	50 year male	Patient had recently recovered from a specific urethritis Ten days before admission a bougie was passed, following which pain developed in left flank, and hematuria Three days before admission, headache, fever, and a *shaking chill Abdominal dis*tension, but no localized tenderness Temperature 107°, white blood count 22,600, urine clear Blood culture positive for Bacillus coli	Plain film negative for stone Cystoscopy revealed normal right ureter but no efflux of urine from left Obstruction was passed at 20 cm up left ureter and a purulent bloody specimen obtained Left nephrectomy Renal vein *contained a parietal adherent* grayish white thrombus	
Aschner (No 4)	36 year male	Large stone removed from right renal pelvis Postoperative course septic and a perinephric abscess was drained Repeated blood cultures showed Bacillus coli	Right nephrectomy No thrombi in the portions of renal vein removed at operation	
Barney and Mintz[43] 1933	31 year female	Phlebitis of both legs following last pregnancy 6 years ago Since then she had had repeated at*tacks of phlebitis first in 1 leg,* then the other Patient was admitted complaining of phlebitis of left leg of 3 weeks' duration, and pain in right flank of 7 days' duration Pain in right flank was dull and persistent, and became worse 2 days before admission Chest negative, abdomen distended with marked tenderness and spasm of right side Temperature was 102.4° and white blood count was 22,600 Urine showed albumin 3+, many red blood cells, and few white blood cells	Patient too ill for cystoscopy Right flank explored under local anesthesia, kidney enlarged, adherent, and dull red color Biopsy showed acute and complete degeneration of tubules and glomeruli Patient ran a septic course Intracapsular nephrectomy Bronchopneumonia and empyema developed of the right chest Death on the tenth postoperative day	Heart normal Thrombosis involved vessels of both legs, iliac arteries, vena cava up to level of left renal vein. Right renal vein occluded by thrombus Thrombi were recanalized in many places Cultures of thrombi negative

TABLE 1—*Continued*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Melick and Vitt[67] 1944	33 year female	Normal delivery 1 month ago. Post-partum course uneventful. One week before admission edema of the left leg developed. This was followed by pain in right chest, dyspnea, chills, and fever. On admission, temperature was 101.8°, heart and lungs negative, abdomen was negative. Left leg 2½ times normal size. Blood culture positive for hemolytic staphylococcus. Patient gradually improved until the twenty-eighth hospital day when she had chill and fever. Urine free from pus and bacteria. On the thirty-eighth hospital day she complained of severe pain in right flank. Examination showed tenderness in right flank; right kidney enlarged 2 to 3 times normal size.	Cystoscopy on thirty-ninth hospital day showed bladder normal and no efflux of urine from right side. Catheter passed up right ureter without difficulty; lavage of pelvis returned old blood and small clots. No excretion of phenolsulphonphthalein from right side. Right retrograde pyelogram showed pelvis poorly visualized, irregularly filled, and somewhat irregular in outline. Lateral pyelogram showed poor filling of pelvis, but no displacement of kidney. Right nephrectomy. Kidney very large, deep purple color, with discrete yellow patches in parenchyma. On section, loss of cortico-medullary markings, and red streaks and flecks were noted in medulla. Large veins contained fresh thrombotic material in which leukocytes were prominent. Renal artery was uninvolved.	
Danhiez[68] 1927	20 year female	Five days after premature delivery, sudden attack of pain in left flank. Pain steady and did not radiate. Patient was admitted 3 days later because of gross hematuria.	Left ureter catheterized; no urine was obtained. Catheter was left indwelling for 10 days. Pain and fever recurred and left nephrectomy was done. Kidney was large and firm and renal markings were obscured. Renal vein contained thrombus.	
Metzler[32] 1928	45 year female	Supravaginal hysterectomy. During the postoperative period, cystitis, left flank pain, and high fever developed. Two days after onset of flank pain, a large, firm, tender mass could be felt in this region.	Cystoscopy revealed cystitis. Both ureters were easily catheterized. Right kidney showed normal function, but no function of left kidney. Left nephrectomy. Kidney showed small infarcts and renal veins were thrombosed.	
Eisendrath[69] 1934	30 year male	Sympathectomy a year before admission because of thrombo-angiitis of left leg. Three weeks before admission, sudden onset of pain in the right flank and hematuria which lasted 48 hours. These symptoms recurred and he was admitted to hospital. Examination revealed a firm, fixed mass in right kidney region.	Cystoscopy showed right ureter easily catheterized, but no urine was excreted on this side. Indigo carmine showed no function of right kidney. Right retrograde pyelogram showed incomplete filling of pelvis and calyces. Right nephrectomy. Kidney dark red color with scattered yellow zones in cortex. Microscopic examination showed that these zones were completely necrotic. Renal vein was filled with a blood clot.	
Blum[70] 1930		Discusses 3 cases which had had recurring attacks of unilateral flank pain and hematuria.	Repeated cystoscopies and pyelography had failed to show a cause for clinical picture. Author did a nephrectomy in each case because of severe bleeding. He found changes in renal vein which resembled cavernous tissue and appeared microscopically be re-canalized venous thromboses.	

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[67] Melick, W. F. and Vitt, A. E.: Thrombosis of the renal vein. J. Urol., 51: 587–596, 1944.

[68] Danhiez, P.: Les Grands Infarctus Renaux. J. d'urol., 23: 481–495, 1927.

[69] Eisendrath, D. N.: Grand Infarctus du Rein. J. d'urol., 37: 47–62, 1934.

[70] Blum, V.: Kavernose Thrombose der Nierenvene. Ztschr. f. Urol., 24: 405–411, 1930.

TABLE 1—*Concluded*

AUTHOR	CASE	CLINICAL BRIEF	UROLOGICAL FINDINGS	AUTOPSY
Muller[11] 1943	14 year male	Patient sustained fractured femur by automobile a year before admission. He had had open reduction and fixation of the fracture. Five days postoperatively phlebitis of both legs developed and left flank pain with hematuria. Because of litigation proceedings he was admitted for study of urinary tract.	Intravenous pyelography showed normal functioning right kidney and no function of left kidney. Left ureter was easily catheterized and ureter filled well during pyelography, but pelvis was only a small disc-shaped affair. Author made diagnosis of destruction of left kidney due to ascending thrombophlebitis from femoral veins.	

arteritis nodosa. Embolism involved other organs in 3 cases. The etiology and source of emboli were unknown in 7 cases. The function of the involved kidney was shown by intravenous pyelography in 10 cases, and indigo carmine in 10, to be very poor or absent in all of 20 cases tested. Return of function in the affected kidney, as shown by intravenous pyelography, required varying lengths of time. It occurred in 4 cases: in 23 days, Ehrstrom[42]; in 28 days, Staehler[8]; in 1 month, Ben-Asher[57]; in 3 months, Richard[61]. In 14 of a total of 18 cases where retrograde pyelography was done, it showed normal configuration of the renal pelvis, calyces, and ureter. Bilateral, total renal infarction was reported by Wosnessensky[34] and Prinzmetal[54].

There was 1 case of septic arterial infarction reported by Pirn[44].

Nephrectomy was done in 11 cases. The diagnosis of renal infarction was made preoperatively in 5 instances (Bull[29], Duvergey and Dax[30], Westerborn[3], Hosel[48], and Cedermark, Lindblom, and Henschen[60]). Metzler[32] and Staehler[8] performed operation for suspected tumor of the kidney. Wildbolz[37], Sheppard[46], and Emmett and Dreyfuss[50] explored kidneys without correct diagnosis before operation. Laparotomy was done 5 times for suspected acute abdominal lesions: appendiceal abscess (Makai[31]), acute cholecystitis (Metzler[32]), and (Barney and Mintz[38]), acute pancreatitis (DesJacques and Boijeau[43]), and spastic ileus (Wosnessensky[34]).

Of 19 cases, the urine contained albumin 1 to 4 plus, and red blood cells and white blood cells in varying amounts. The urine was reported negative in 1 case.

INCIDENCE

Barney and Mintz[38] studied 143 autopsy records in which renal infarction was reported, and noted that most cases occurred between the ages of 30 and 50 years. There was no predominance of either sex. The diagnosis had not been made clinically, and there had not been a urological study made in any of them. There was cardiac disease in 95 per cent of the cases in which the observation was recorded.

Westerborn[3] notes the study by Schildt at Upsala where he found 106 cases of renal infarction in 6,328 post-mortem examinations. He included small and large infarcts in the report. Of the 106 cases, only 9, or 8.5 per cent, had recorded clinical symptoms that suggested renal artery embolism. The infarction was bilateral in 40 per cent of the cases.

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[11] Müller, A.: Verlust der linken Niere durch aufsteigende Venenthrombose. Schweiz. med. Wchnschr., 24: 998–999, 1943.

Hoxie and Coggin[47] studied the protocols of 14,411 autopsies and found renal infarction was diagnosed clinically in only 2 of the cases. In 76 per cent of the 205 cases of renal infarction found in these autopsies, definite cardiac lesions were present. Of 242 cases with bacterial endocarditis, 55, or 23 per cent, had embolic infarction of the kidneys. Bilateral infarction was found in 102 cases, in the right kidney alone in 42, and in the left kidney 56. In the series, healed infarcts were found in 25 per cent. Of the types of cardiovascular disease associated with renal infarcts, rheumatic heart disease with or without aricular fibrillation, occurred in about 16 per cent. Acute and subacute bacterial endocarditis, coronary occlusion with mural thrombi, and sclerosis of the aorta or renal arteries each occurred in about 16 per cent.

CASE REPORTS

Case 1. J. R., a 50 year old white male, was first admitted to another hospital on June 17, 1946, and discharged on July 3. A diagnosis was made of nonfunctioning left kidney and rheumatic heart disease. An extract, obtained from the hospital record, follows:

The temperature on admission was 102.4°, pulse 100 and irregular. His chief complaint was severe pain in the left flank and upper abdomen which occurred suddenly, awakening him at 3 o'clock in the morning of June 16, 1946. The pain was steady, did not radiate, and later settled in the left lumbar region. The patient had no nausea, vomiting, or urinary symptoms. He did have hiccoughs.

On examination, the heart was enlarged to the left, and sounds were completely irregular. No murmurs were heard. There was tenderness in the left flank, and the left kidney was palpable. Blood pressure was 160/110.

Intravenous pyelography (fig. 1,*A*) showed non-functioning left kidney and normal functioning right kidney. Left retrograde pyelogram (fig. 1, *B*) showed a rather large kidney with normal appearing calyces, pelvis, and ureter.

By the second hospital day the pain had markedly diminished and temperature was 99°, gradually becoming normal by the eighth hospital day.

The laboratory findings on June 18, 1946 showed the white blood count to be 24,300. Urine was acid, cloudy, dark amber, 1.026, albumin 4 plus, sugar 0, diacetic 0, bile 0, sediment loaded with red blood cells and many white blood cells, and culture showed no growth. Blood sugar was 86. Nonprotein nitrogen was 42 mg. per cent. Chest x-ray showed large heart shadow and increase in vascular markings.

Laboratory findings on June 20 showed a white blood count of 17,700. Urine showed sediment with 50 red blood cells, 10 white blood cells, and epithelial cells. Blood Hinton was negative and blood culture showed no growth.

Laboratory findings on June 27 showed urine from left kidney loaded with red blood cells and many white blood cells. Stained smear showed no organisms, and the urine culture was negative.

The patient was first seen by us on July 14. He was worried about the possibility of tumor in the nonfunctioning left kidney. He complained of occasional, slight discomfort in the left flank since the severe pain had disappeared. He had no specific urinary complaints. The past history was essentially negative, except for cholecystectomy in September 1938, and exploration of the common duct in May 1939. He had had auricular fibrillation for 12 years and had been taking 1 digitalis pill a day.

The heart was enlarged and completely irregular in rhythm. The abdomen showed some tenderness in the epigastrium and left upper quadrant on deep palpation. The kidneys were not palpable.

Cystoscopy showed urine cloudy, bladder normal except for a few ecchymotic areas in the trigone and around the left ureteral orifice. Both ureters were catheterized without meeting any obstruction. There was good flow of urine on the right, but poor flow of very pale, cloudy urine on the left. The phenolsulphonphthalein test showed an excretion of 20 per cent of the dye in 3 minutes on the right, and less than 5 per cent in 8 minutes on the left.

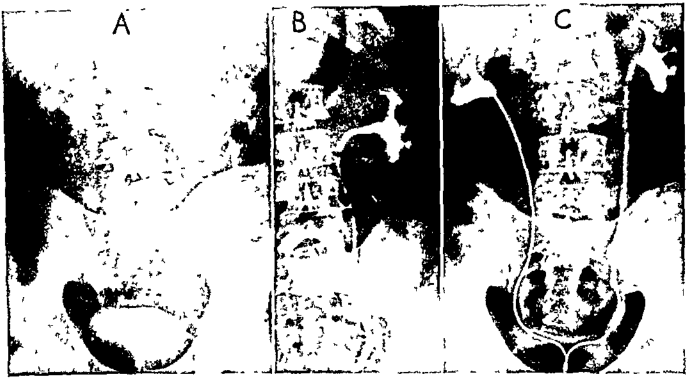

Fig. 1 Case 1. *A*, Original intravenous urogram, showing absence of function of left kidney. *B*, Original retrograde pyelogram, showing normal calyces, pelvis and ureter. *C*, Bilateral retrograde pyelogram 1 month after onset, showing normal pyelography except for incomplete filling of upper third of left ureter, which was due to edema.

Retrograde pyelogram (fig. 1, *C*) showed normal pelvis, calyces, and ureter on right, following injection. On the left, the lower half of the ureter was slightly dilated, the upper two-thirds showed thickening of the wall, and the dye formed an irregular density in the ureter. There was a slight irregularity in contour and outline of the superior major calyces. Interpretation: "Tumor involving upper left ureter and superior calyces."

The laboratory findings showed blood count normal, blood sugar 80, and nonprotein nitrogen 33 mg. per cent. Urine was acid, 1.010, slightest possible trace of albumin, occasional red blood cells, and loaded with white blood cells. Bladder sediment showed occasional red blood cells, 15 to 20 white blood cells, and the culture showed enterococcus. The right kidney showed rare white blood cells and a negative culture. The left kidney showed rare red blood cells, 7 to 8 white blood cells, and no growth in culture.

The patient underwent left ureteronephrectomy on July 31, 1946. There was edema of the fatty bed (fig. 2), and the kidney was quite firm. There were adhesions at both poles of the kidney. The outer surface of the kidney was granular and the fat was adherent. The cut surface showed, in the lower half of the kidney, 4 pyramids ivory white in color, which had lost all normal markings. At the upper pole was another isolated pyramid of exactly the same type. The cortex over these pyramids was granular and discolored to a yellowish brown.

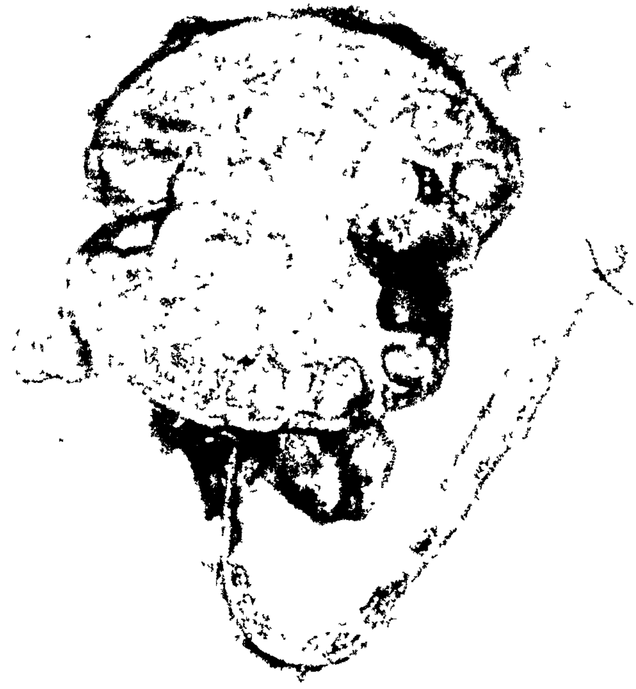

FIG. 2. Case 1. Left kidney split open, showing infarcts in lower half and at upper pole. Note edema of perirenal fat and of ureter.

The tissue between these areas was what appeared to be entirely normal pyramids and cortex. The ureter showed edema and a few red areas of a traumatic nature, but no papillary tumor. Microscopic section of these ivory white areas showed loss of all renal architecture, with a few areas of normal-appearing glomeruli. There were thrombi in the interlobular and arcuate arteries (fig. 3). Near the periphery there was an increased amount of interstitial tissue, and the capillaries were dilated and engorged in this region. Examination of the uninvolved area showed the vessels free of thrombi and the tissue appeared normal (fig. 4).

Except for hiccoughs and abdominal distension for a few days the postoperative course was excellent.

The laboratory findings on July 29 showed blood count normal, blood nonprotein nitrogen 35 mg. per cent, and the urine showed albumin 2 plus, 1 014, acid 0, sugar 0, and 10 to 12 white blood cells

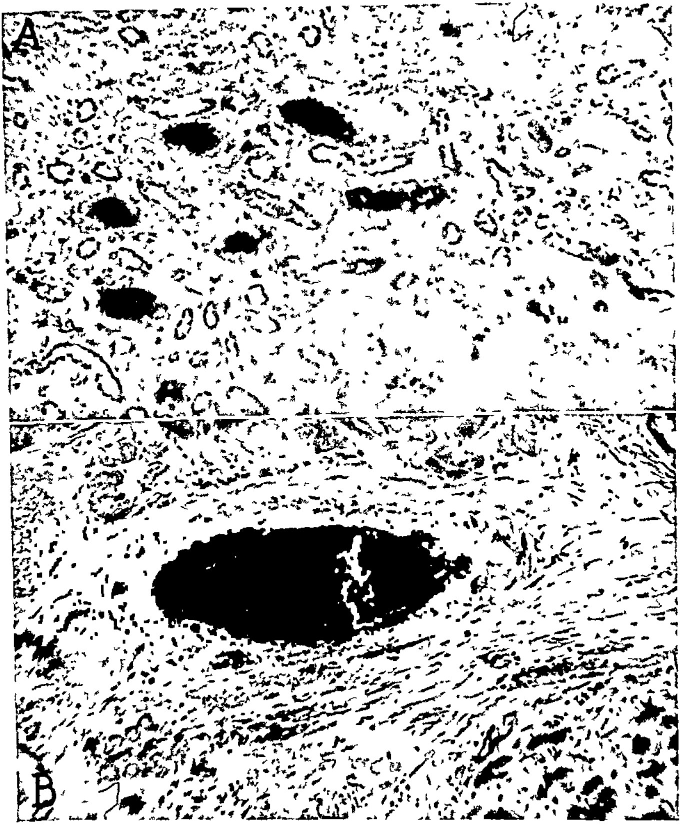

Fig 3 Case 1 *A*, Infarcted pyramid, showing necrosis and thrombosed intralobular arteries *B*, Showing thrombosed arcuate artery

The patient was discharged from the hospital on August 15.

Examination at the office on August 30 showed the patient to be free of symptoms and with no complaints The wounds were well healed. Urine showed no albumin and a negative sediment. Urine culture showed aerobacter aerogenes.

On the most recent examination, March 12, 1947, the patient stated that he was working hard and had gained 6 pounds Blood pressure was 130/78. The pulse was irregular, but there was no pulse deficit. Heart sounds were of fair quality with an early diastolic murmur at the apex. The urine showed 1.014, acid, albumin 1 plus, sugar 0, and sediment negative. Phenolsulphonphthalein, collected in 4 fifteen-minute excretion periods, showed 52 per cent output. The nonprotein nitrogen was 33 mg. per cent.

Case 2. Mrs. S. W., a 56 year old white woman, was admitted to the hospital on August 13, 1946. About noon she had been seized with severe pain, located in the left lumbar region and in the left upper quadrant of the abdomen. She felt faint, perspired freely, and vomited. She was seen by her local doctor a few hours later, and sent to the hospital.

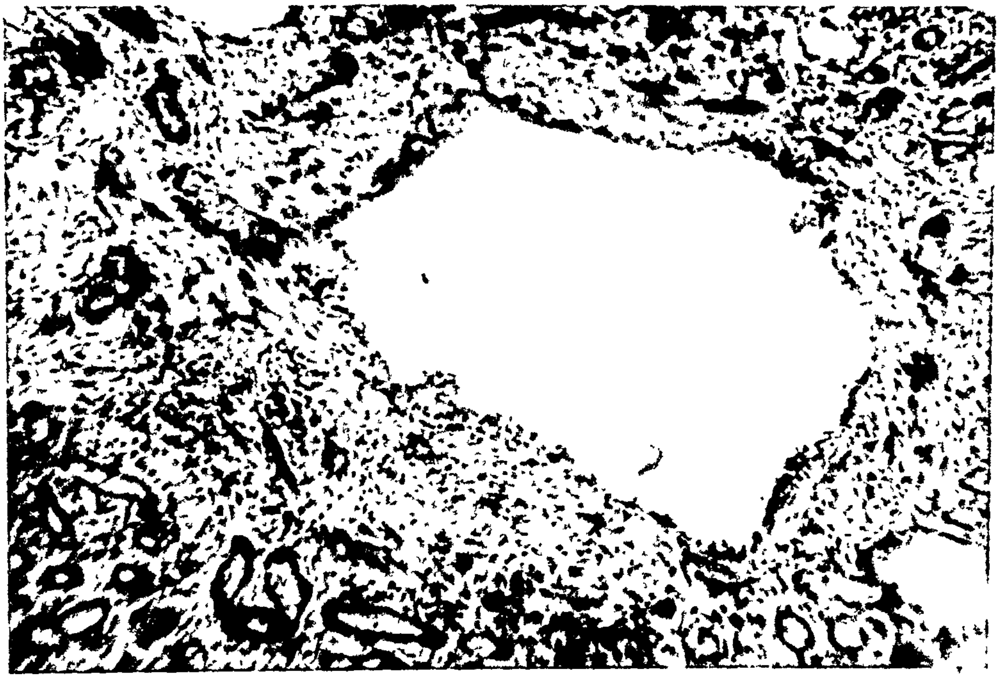

FIG. 4. Case 1. Showing normal arcuate artery from same kidney

The past history revealed that in January, 1946 acute shortness of breath developed and her doctor kept her in bed for about 3 months because of a tired heart. She had been taking 1 digitalis pill daily since. She had lost 30 pounds during the last year, apparently because of poor appetite. There was no history of rheumatic fever.

The heart was enlarged to the left. There was a questionable pre-systolic thrill at the apex. The blood pressure was 198/100. The abdomen showed some generalized distention and tympany. There was no localized tenderness and no masses were felt. There was no peripheral edema.

For the first 10 hours after the patient was admitted into the hospital, the generalized abdominal pain and vomiting continued. A surgical consultant did not find signs of any acute surgical condition. During the next 48 hours leukocytosis and fever developed, and the tenderness became more marked in the left flank. On August 15 there was dullness over the base of the left lung, extending upward to inferior angle of the left scapula. There was diminished vocal fremitus and breath sounds in this area. The patient had no respiratory or urological symptoms. The temperature varied from 99 to 102.6° for about 2 days, and gradually came to normal by the seventh hospital day. The patient was given penicillin, in units of 20,000, every 3 hours for several days after admission. On August 21 most all signs of fluid at the base of the left lung had gone, the temperature had nearly subsided, and there was no more tenderness in the flank. The chest x-ray was reported negative on August 26, 1946.

Intravenous pyelography on August 27, 1946 showed nonfunctioning left kidney and a normal right kidney (fig. 5, *A*).

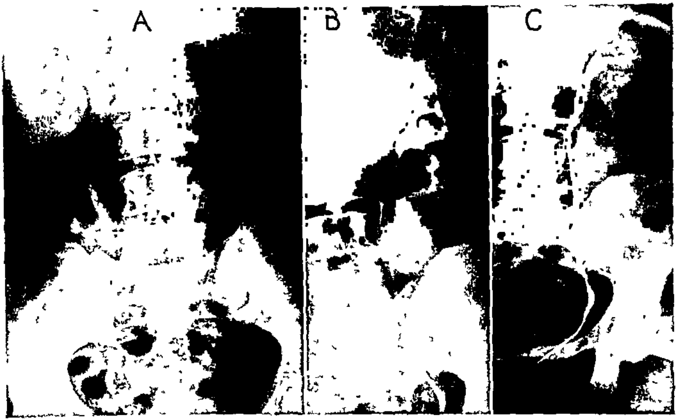

FIG 5 Case 2. *A*, Intravenous urogram, showing absence of function of left kidney. *B* Retrograde pyelogram, showing normal calyces, pelvis and ureter Moderate pyelovenous backflow. *C*, Retrograde pyelogram made 7 months later, showing atrophy of calyces at site of infarction

Cystoscopy on August 29 showed clear urine and a normal bladder. Left ureter was catheterized without meeting obstruction. Drainage was very diluted and clear. The phenolsulphonphthalein appearance time was 3 minutes, with pale color. A left retrograde pyelogram showed good filling of calyces, pelvis, and ureter (fig. 5, *B*). A moderate degree of pyelovenous backflow was present.

On August 13 the blood count was: hemoglobin 18.4 gm., red blood count 5,800,000, white blood count 15,000, and polymorphonuclear leukocytes 77 per cent. August 14: hemoglobin 20.5 gm., white blood count 25,100, and polymorphonuclear leukocytes 71 per cent. August 15: hemoglobin 17.8 gm., white blood count 31,600, and polymorphonuclear leukocytes 74 per cent. August 22: hemoglobin 14.6 gm., red blood count 4,890,000, white blood count 14,100, and polymorphonuclear leukocytes 66 per cent. The blood culture on August 16 showed no growth.

On August 13 the urine showed: acid, 1.020, slightest possible trace of albumin, and no sugar. Sediment showed occasional white blood cells and no red blood cells. August 15: acid, 1.010, 2 plus albumin, and no sugar. Sediment showed occasional white blood cells and 4 to 5 red blood cells. August 22: alkaline, 1.012, no albumin or sugar. Sediment showed 5 to 7 white blood cells and no red blood cells. August 29: stained sediment from bladder showed gram positive cocci. Stained sediment from left kidney showed no organisms. Bladder culture showed enterococci. Culture from the left kidney showed atypical Pseudomonas aeruginosa.

The patient was discharged from the hospital on August 30.

Intravenous pyelography on January 18, 1947, showed a normal functioning right kidney and no function on the left.

On March 3, 1947, the patient's only complaint was that she became rather tired at the end of the day. Physical examination showed: blood pressure 168/80, both arms; pulse 96, full, regular rhythm; lungs negative. Heart: apex felt in fifth interspace, lateral to the midclavicular line. First sound was accentuated, pulmonic 2 was greater than aortic 2. Abdomen: soft, flat, no tenderness, and no mass. Lower pole of right kidney was palpable.

Cystoscopy on March 4 showed left ureter readily catheterized with a ready flow of fairly normal-appearing urine.

Left retrograde pyelogram showed the inferior calyx to be smaller and somewhat contracted, as compared with original examination (fig. 5, *C*).

Laboratory findings: blood count normal, blood nonprotein nitrogen 35 mg. per cent, sugar 0. Urine: acid; sugar 0; acetone 0; white blood cells, 5 to 6; and a few epithelial cells. Urine sediment from left kidney showed a few clumps of white blood cells and no bacteria. Culture from bladder and left kidney showed hemolytic staphylococcus aureus and enterococci. Phenolsulphonphthalein: 3 per cent of dye from left kidney, and 25 per cent of dye from right kidney, collected from bladder.

Case 3: Mrs. L. L., a 64 year old white woman, was admitted December 2, 1946. About a year and a half previously, because she was losing weight, she had a medical examination. X-rays showed an enlarged left kidney at that time. Her only urinary complaints were recurring attacks of frequency and burning on urination, of 5 years' duration. These attacks usually came on suddenly and would last for several days. Bed rest and forcing fluids gave her relief.

Past history revealed that in 1937 she had had a sudden severe attack of pain in the lower left side of her chest, accompanied by shortness of breath. A diagnosis of spontaneous pneumothorax was made then. In 1938, she awoke from sleep gasping for breath and had no accompanying pain or fever. Her local doctor told her she had had a heart attack and she was kept in bed for 12 weeks. Following this, for several months, she had shortness of breath on exertion and couldn't do her housework. There had been no hemoptysis or dependent edema. Patient states that her blood pressure was low at this time. She has not had any marked dyspnea or palpitation during the past few years.

Intravenous pyelography showed normal pelvix, calyces, and ureter on the right. On the left there appeared to be a mass about the size of a 25 cent piece in the upper pole, splitting the upper calyces (fig. 6).

Physical examination showed heart with sounds of fair quality, rhythm regular, a rather rough systolic murmur at the apex and base, and loudest over the aortic area. The blood pressure was 125/80. The abdomen showed no tenderness or masses. The liver, kidneys, and spleen were not palpable.

The blood count on December 3 was: hemoglobin 12.2 gm., red blood count 3,890,000, white blood count 7,300. Urine: acid, 1.011, albumin 0, sugar 0, 3 to 4 white blood cells. Blood sugar 131. Blood nonprotein 35 mg. per cent. December 4: blood sugar 95. December 5: blood Hinton negative.

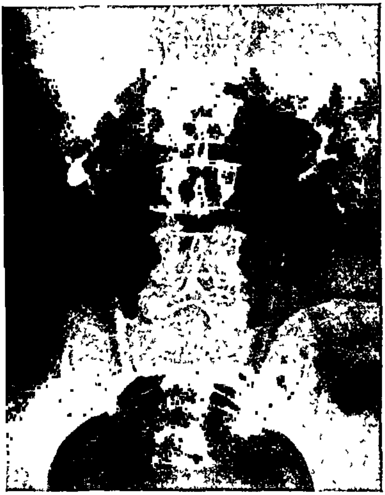

FIG 6 Case 3. Intravenous pyelogram, showing defect at upper pole which proved to be cyst in infarct.

Preoperative diagnosis of cyst or tumor was made.

Operation, December 4, 1946: The kidney was freely movable and appeared to be normal except for the fact that, at the upper pole, on the outer curvature, there was a puckered area having all the appearances of an infarct. Beneath this area could be palpated a cyst about the size of a quarter. The infarct and cyst were excised. The cyst contained light amber-colored fluid and had a smooth, gray lining and a flexible thin wall (fig. 7).

Microscopic examination: There was atrophy of the parenchyma and an increased amount of fibrous tissue around the cyst. The picture was that of arteriosclerosis with retention cyst.

The postoperative course was uneventful except for retention of urine which cleared readily after a few days of constant drainage. The patient was discharged on December 23, 1946.

The patient was seen again on February 5, 1947 at the office. She had no complaints and was in excellent condition.

Case 4: A 40 year old housewife, who was 5 months pregnant, was admitted with complaint of severe left flank pain. She felt well until 48 hours before admission when she had sudden onset of pain in the left flank. The pain was steady and very severe, and repeated injections of morphine gave only partial relief. Physical examination revealed aortic insufficiency, mitral stenosis, and auricular fibrillation. The left flank was exquisitely tender, the abdomen was symmetrically enlarged, and the uterus palpable at the level of the umbilicus. The temperature was 99.5°.

On cystoscopic examination the bladder was normal. There was an intermittent efflux of clear urine from the right ureter, but no efflux from the left. A catheter was passed to the left kidney without meeting any obstruction, and a clear flow of urine was obtained. The patient had immediate relief of pain. A plain urogram showed an opaque shadow which looked like a calculus and was in the line of the catheter. The catheter was left indwelling. The ureteral catheter came out the next day and the pain in the left flank returned. Two days after admission, the left kidney and ureter were explored. The ureter was mobilized and found to be normal. There was edema of the fatty bed and the kidney felt very soft in the upper half. Only the lower third of the kidney appeared normal. A biopsy of the parenchyma in the upper half of the kidney confirmed the clinical diagnosis of renal infarction. The postoperative course was excellent and the patient had no recurrence of pain after operation. (This case is presented through the courtesy of Dr. J. Hartwell Harrison.)

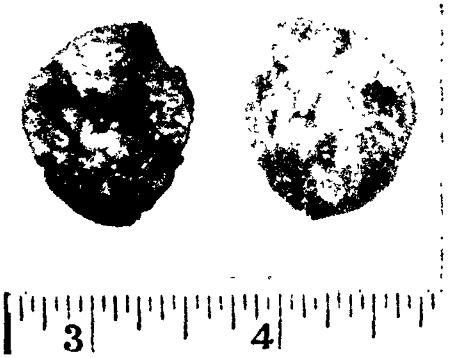

FIG. 7. (Left), Surgical specimen, external surface, showing umbilication of true capsule over cyst; (right), internal surface of infarct, showing point of attachment of cyst.

DISCUSSION

The material collected for analysis consists of 20 cases of renal infarction in which cystoscopic study was not made, 70 cases with modern urological study, and the 4 here reported, for a total of 94 patients. They comprise all age groups from infancy to the aged. Although analysis of the 2 main groups has been made separately, the essential findings are similar, but more complete where cystoscopic studies were made.

Renal infarction includes 3 classes of patients: arterial infarction, venous infarction, and traumatic infarction. These 3 types of lesions differ in many ways and will be considered separately. Small degrees of venous infarction is encountered in some tumor and other surgical lesions of the kidney. It appears to be true that such conditions are overshadowed by the symptomatology of the major condition and are findings of the surgical pathologist.

Arterial infarction. Of the 94 cases of infarction of all kinds, there were 71 instances of arterial infarction. Most of these were sterile infarcts. In some the infarction was bilateral and extensive. In others the infarction was unilateral, but of varying degrees of extent. In some, infarction involved only portions of one kidney. The fate of the patient rests on the bilateral occurrence of the lesion and the integrity of the other kidney when but one kidney is involved. On the whole, if left alone, sterile infarcts heal with damage to the involved portion of the kidney or shrinkage of the organ, if infarction is complete. Cystic degeneration of infarcted areas occurs. Such cysts may be mistaken for tumor. It appears to be true that renal function is greatly damaged irrespective of the degree of infarction, for a time, but that return of renal function to undamaged parts may be expected.

The diagnosis of arterial infarction rests on the following points: 1) Sudden onset of pain in the flank or upper abdomen. 2) The demonstration of a nonfunctioning kidney on the involved side by intravenous pyelography, and by failure of excretion tests. 3) The finding by retrograde pyelography of normal pelvis, calyces, and ureter on the affected side. 4) The presence of disease of the heart or blood vessels. 5) The presence of albumin in abnormal amounts in the urine, together with microscopic and sometimes gross hematuria.

In previously normal kidneys, cystoscopy shows no disease in the bladder and the ureters are easily catheterized. A plain film is negative for stone. Retrograde pyelography shows normal calyces, pelvis, and ureter. The phenolsulphonphthalein test shows no dye or only a faint trace from the affected side. Bladder urine culture, and culture of the kidney urine are negative. No bacteria are present in the stained sediments. When infarction occurs in abnormal or diseased kidneys, the above facts are modified by the fundamentals of other disease.

Yet, the pyelographic evidence produced in cases of infarction tends to lead one to interpret abnormalities in pyelography in terms of better known disease. In the first case reported here, edema of the ureter was mistaken for papillary tumor, and in the fourth case, a filling defect in the ureter led to the diagnosis of stone. Folsom was misled by pelvic and calyceal distortion to make a diagnosis of renal tumor. These are but samples of the basis for erroneous diagnosis encountered in the literature.

Diagnosis of renal infarction may be demanded in kidneys which were the seat of previous infarctions. In both experimental and clinical data it has been shown that cystic degeneration of old infarcts occurs. In the third case, this led to diagnosis of renal tumor. It is to be remembered that the characteristic end result of infarction is calyceal shrinkage, as shown in case 2. This observation may help in differential diagnosis in such kidneys when they are acutely infarcted.

It appears to be a fact that total, or near total, loss of function in the affected kidney is a primary diagnostic item in infarction. This loss of function seems to occur irrespective of the degree of involvement of renal tissue. Such loss of function is temporary. Partial, or apparently even complete, return of function occurs within a few weeks or several months. The degree to which function returns is dependent on the amount of kidney tissue damaged. Where total infarction occurs in the absence of infection, the end result is complete renal atrophy, as shown in Foley's case[45]. Ben-Asher[57] noted transient hypertension in infarction.

Septic emboli to the kidney in endocarditis do occur occasionally (1 case in 67) in acute phases of that disease. Procedure will depend on the degree of renal sepsis and the condition of the patient.

Venous infarction. Venous infarction is a much more serious disease than aseptic arterial infarction. Clots are more often infected, and the condition is either bilateral or apt to become so by extension of the original process of thrombosis. Of 20 cases reported in the literature, 8 died. The condition was unilateral in 16. Twelve had nephrectomy, from which all survived. Four bilateral and 4 unoperated unilateral patients died.

The clinical picture of renal infarction, due to venous thrombosis or occlusion, differs from that of arterial renal infarction in the following manner: 1) It is associated with septic states: pneumonia, enteritis, puerperal infection, severe pyelonephritis, pyemia, or it follows thrombophlebitis of the leg veins or vena cava. 2) The kidney is greatly enlarged and is often palpable. 3) There is gross hematuria in most cases, and occasionally perirenal hemorrhage. 4) Retrograde pyelography usually shows deformity and incomplete filling of the calyces and pelvis. 5) The condition runs a progressive and septic course, and most cases do not recover unless nephrectomy is done. Of the 20 venous infarctions, 5 occurred in infants and were associated with severe gastro-enteritis in 4 instances, and with bronchopneumonia in 1. In each case a mass could be felt in the involved side and there was gross hematuria. Retrograde pyelography was done in 2 instances and showed no filling of the pelves and calyces. Two infants, unoperated, died and 3 survived following nephrectomy. The urine contained large amounts of albumin, pus, and blood. In the 2 year old girl reported by Fahr[65], death was caused by pyemia originating in an abscess at the groin. She became anuric a few days before death and the autopsy showed extension of an infected thrombus from the iliac vein into the vena cava and both renal veins. The 4 cases reported by Aschner[62] were incident to septic states. The first case died of bilateral pyonephrosis complicating prostatic obstruction. The second case died of staphylococcal septicemia and had cortical abscesses in the left kidney. The third case had chill, fever, and left flank pain, following urethral instrumentation, and recovered after nephrectomy. The fourth case had had a pyelolithotomy followed by a perinephric abscess which was drained. Nephrectomy was done, but no thrombi were present in the portions of the renal vein removed at operation. The cases reported by Barney and Mintz[33] and by Melick and Vitt[67] occurred during an attack of thrombophlebitis of the femoral vein. Danhiez'[68] case began 5 days postpartum. Metzler[32] described a case occurring after a supravaginal hysterectomy. The case observed by Eisendrath[69] had a history of thrombo-angiitis obliterans. Blum[70] did a nephrectomy in 3 cases which had had recurrent attacks of severe flank pain and hematuria. The renal veins in these cases were enlarged and looked like cavernous tissue and microscopic examination showed recanalized venous thrombi. Muller[71] reported a case occurring 5 days after open reduction and fixation of fractured femur. The case reported by Derow, Schlesinger, and Savitz[66] showed clinically the signs of a nephrosis until there occurred signs of obstruction of the inferior vena cava. Renal function remained good until death from peritonitis 13 months later. Autopsy showed old recanalized thrombi of both renal veins and the vena cava, but there was no intrarenal thrombosis. In all but 1 case, the pain began suddenly and was located in the renal area. Gross hematuria occurred in half the cases. A mass was felt in the kidney area in 10 cases. Chills and fever were present in 13 cases. Nephrectomy was done in 12 cases. All the others died of sepsis or renal failure, due to extension to the opposite kidney. Cystoscopy showed no efflux of urine from the involved kidney in 6 cases. Retrograde pyelography showed incomplete filling and distortion of the pelvis and calyces in the 4 cases where done.

Venous infarction may be suspected clinically by the following symptoms and signs: 1) Sudden onset of pain in the renal area, accompanied by hematuria. 2) The presence of acute infection such as a gastro-enteritis, pneumonia, puerperal sepsis, or of phlebitis of the femoral veins. 3) The occurrence of a tender mass in the kidney area. 4) Chills and fever and progressive decline in general condition. 5) Retrograde pyelographic demonstration of incomplete or irregular filling of the pelvis and calyces.

Traumatic infarction. Traumatic infarction is much more rare than arterial and venous infarction. Of the 3 cases reported, 2 were unilateral and 1 bilateral. That reported by Hirshberg and Soll[58] had pain in the flank, and hematuria, following accident, and a mass could be felt in the kidney area. Nephrectomy showed hemorrhage around the pedicle and there were scattered areas of necrosis in the kidney. Rexford and Connolly's case showed absence of function by intravenous pyelography, but retrograde pyelography showed normal calyces, pelvis, and ureter. The urine was clear, except for large amounts of albumin. Nephrectomy showed 3 triangular infarcts comprising about half the total renal tissue. Barney and Mintz'[38] case was an autopsy case. There were infarcts in both kidneys.

SUMMARY

Arterial, venous, and traumatic infarction of the kidney are diagnostic and surgical entities encountered with some frequency. An analysis of reported cases indicates certain characteristics of each form of infarction from which diagnosis may be made, if the condition is considered in the differential diagnosis.

Sterile arterial infarction is most common of the 3 types. It seldom, if ever, requires surgery. Operation is frequently done for sterile infarct, through mistaken diagnosis. Septic arterial infarction is rare. Surgery is indicated. Chronic infarction tends to undergo cystic degeneration occasionally. Arterial infarction is closely associated with cardiac disease.

Venous infarction is a serious condition. Its close association in origin with septic states, and the almost invariably infected clots, makes surgery imperative when unilateral. Venous infarctions frequently, and arterial infarctions occasionally, are accompanied by large subcapsular or pararenal hematomas. Even in the absence of hematoma the kidney is enlarged.

Traumatic infarction forms but a small portion of the reported cases (3 cases). It is dependent on direct injury to the vessels.

The most important single item in diagnosis of acute infarction of the kidney is complete, or almost complete, loss of function, almost irrespective of the degree of tissue involvement, in kidneys in which pyelography remains unchanged. Chronic infarction is recognizable in proportion to the caliceal atrophy which results from the infarct in its scar stage.

Clinical studies of infarcted kidneys parallel closely established experimental work.

DISCUSSION

Dr. John K. Ormond (Detroit, Mich.): This paper is of that quality which we have learned to expect in anything with which Granville Crabtree has had anything to do. The authors have made a careful review of the literature of renal infarction and an analysis of the cases reported. I believe they have performed a service to us in focusing our attention on this subject. I presume I am not exceptional in that while I have been aware of this condition and have met it occasionally I have not paid a great deal of attention to it.

In preparation for this discussion I have done three things: 1) I have reviewed the autopsies done at the Henry Ford Hospital during the 10 year period between 1926 and 1936. There were 1766 autopsies, and renal infarcts were found in 95 instances, some of which were old healed infarcts and some of recent origin. The conditions most often responsible for the infarcts were in order of frequency: vegetative endocarditis, mural thrombi, general arteriosclerosis, peripheral thrombosis, and chronic nephritis.

2) I have reviewed the records of the patients in whom the diagnosis of renal infarct was recorded clinically in the 25 year period between 1926 and 1946. There were 52 cases and a heart condition was responsible in 43 of them. The lesions met with were, in order of frequency: rheumatic heart disease, 18; hypertensive heart disease, 11; bacterial endocarditis, 10; arteriosclerotic heart disease, 8; and coronary occlusion 7. Auricular fibrillation occurred in 15 and myocardinal insufficiency in 14.

In the 9 instances in which no cardiac condition was present, the diagnoses were as follows: 1) hypertension, nephrosclerosis, syphilis; 2) hypertension, subarachnoid hemorrhage; 3) hypertension, marked; 4) carcinoma of the liver; 5) carcinoma of the liver, diabetes, and bronchopneumonia; 6) thrombophlebitis, lower extremity; 7) septic thrombophlebitis of lower extremity; 8) acute infectious arthritis of the knee, staphylococcus bacteriemia; 9) streptococcus septicemia and tuberculous peritonitis.

In this series 35 were in males and 17 in females. Twenty-seven died during the hospital admission in which the infarction occurred and the lesion was found at autopsy in 20—no autopsy being done in the other 7.

3) I have reviewed the records of the patients with renal infarcts seen by the Division of Urology, usually in consultation, in the 20 year period between 1926 and 1946. There were 10 such patients—4 of whom were examined cystoscopically and 1 by intravenous pyelography. Diagnosis of renal infarct was made in 8 out of the 10—later confirmed at autopsy in 2. The diagnosis was made at operation in 2. Of the 2 patients in whom the diagnosis was not made, one was in extremis when seen and in the other an infarcted kidney was found at operation but not recognized as such until seen at autopsy.

Three of these patients were operated on by the urological division under mistaken diagnoses: 1 patient with hemolytic streptococcus septicemia had the right kidney explored for abscess or perinephric abscess. At autopsy infarction of the kidney was found though it had not been recognized at operation.

Another patient with acute infectious arthritis of the knee and staphylococcus bacteriemia was thought to have perinephric abscess, but at operation a renal infarct was found.

The third was a patient with rheumatic heart disease and auricular fibrillation. Stone in the kidney was the preoperative diagnosis because of a shadow seen in the x-ray. At operation no stone was found and 12 days later he died, autopsy showing a renal infarct.

The authors divide the cases into three groups—arterial, venous, and traumatic. I have never seen a case of traumatic renal infarct—and undoubtedly these would be most likely to be seen by the coroner.

Venous infarcts are much more rare than the arterial variety. It was never diagnosed clinically by us—and among the autopsies we reviewed we found only 2—in 1 of which there was direct extension from iliac veins to vena cava to the renal veins. In the other there was thrombosis of the renal veins associated with thrombosis of the superficial veins in the inguinal region, but the connection between them was not clear. We have found arterial infarcts associated with peripheral venous lesions in the presence of a patent foramen ovale.

The authors give 5 points for the diagnosis of arterial infarction, which is the most common form. The symptoms are those of an acute renal lesion—stone, obstruction, infection—and I do not believe complete urological investigation is always or even usually indicated. In the presence of grave disease of the heart or blood vessels, that is in four-fifths of the cases, watchful waiting with a tentative diagnosis of infarct may be preferable to extensive manipulation, for neither the infarction nor the conditions with which it may be confused are likely to have immediate serious consequences in themselves, the underlying condition being the serious matter. However, this does not minimize the importance of these criteria for diagnosis, for in the 20 per cent of cases which occur in the absence of grave vascular disease, there may be nothing to point towards a probable diagnosis of infarct, and diagnosis cannot be made without complete urological investigation.

Venous infarction is a different matter. I have had no experience with it, but the authors have analyzed a good series and have given criteria for its diagnosis, and since the condition itself is exceedingly serious and life may depend on prompt operative treatment, every means at our disposal should be used to make the diagnosis; and the same may be said of the traumatic variety.

I have enjoyed Dr. Regan's paper and profited much from it.

Dr. S. E. Kramer (New York, N. Y.): Renal infarction caused by the blocking of the blood supply to smaller or larger areas of kidney parenchyma is almost always an indication of most serious cardiac and vascular disease. Barney and Mintz reported necropsy findings showing the association of renal infarction with extensive widespread thrombosis of the venous and arterial systems. Aschner reported his own and other recorded cases which simulated surgical renal disease, but which were cardiac in origin. He mentioned other causes such as thrombosis in the renal artery or its branches caused by trauma, acute arteritis, chronic arteritis, atherosclerosis and periarteritis nodosa. He emphasized that the differential diagnosis includes acute surgical conditions, calculus, tumor, filling defects as produced by a clot and conditions of renal pain as may be produced by torsion of the vascular pedicle of a floating kidney.

Massive unilateral renal infarction complicating abdominal surgery and occurring spontaneously have been reported by Emmett and Sheppard with the performance of nephrectomy and cure.

Recently Loomis has produced hypertension in rats by the ligature and cutting of smaller and larger renal blood vessels with production of infarction. She found that partial infarction of one kidney was followed more promptly by hypertension than was total infarction of one kidney. She concluded that necrotic renal tissue is the source of vasopressor agents which are absorbed into the blood stream. Fishberg has reported hypertension due to renal embolism. In addition, aortography has been advocated as an aid in the diagnosis of renal infarction. It seems to me that these considerations should alert urologists to the recognition of unilateral renal infarction produced by localized pathological changes in the blood vessels of one kidney and where such involvement is not associated with serious disease elsewhere in the cardiovascular system nephrectomy must be considered.

Two such cases have occured in my own practice in the past 3 years and both were treated successfully by nephrectomy. The first was explored as a possible papillary neoplasm of the renal pelvis and the second was strongly suspected because of the clinical course.

M. F., a white female aged 34, was admitted to Polyclinic Hospital. She was luetic. For 1½ years she had had attacks of severe pain in the right loin. The past attack had lasted 3 weeks requiring hypodermics to control the pain. The right kidney was palpable and tender. Indigo carmine appeared from the right side in 10 minutes, 1 plus concentration; left side, 6 minutes, 4 plus concentration. Pathological report: Multiple hemorrhagic infarcts of kidney with necrosis and hemorrhagic interstitial nephritis; 2 small renal calculi.

A. U., a white male aged 40, was admitted to the Polyclinic Hospital to undergo pyelotomy for a calculus obstructing the left ureteropelvic junction. At the time of operation the pelvis was found to be entirely intrarenal. Delivery of the kidney was accompanied by considerable rotation, but the stone was removed without much difficulty. On the third postoperative day the temperature suddenly rose to 106 degrees and it was noted that no urine had drained from the kidney wound. In the following days a profuse bloody non-urinary drainage occurred from the wound. The drainage gradually became serosanguinous and the temperature gradually came down. For 6 weeks postoperatively the drainage of this material continued and a low-grade temperature persisted with occasional elevations despite penicillum of sulfa medication. The voided urine was clear and free of cellular elements. At the end of 6 weeks a study was made, since a necrosis of the kidney was suspected due to vascular impairment. Pathological report: Suppurative nephritis with extensive necrosis.

Nephrectomy was carried out in both instances with prompt clinical improvement. Both patients are living and apparently well at the present time.

DR. FRANCIS C. REGAN (Boston, Mass.): The last case of dissecting aneurysm gives clinical signs which might be confused with renal infarction. However, neurological signs, changes in the circulation in the extremities, changes in blood pressure and local examination might give you a lead. I would say, in reference to hypertension, that clinically hypertension has been found to occur in a certain percentage of these cases, but it has been transient. The function does return in these kidneys that have been assaulted by infarcts, provided it has not been complete or total.

I especially would like to thank Dr. Ormond for his kind remarks.

TUBULE ADENOMA OF THE KIDNEY[1]

BENJAMIN S GORDON

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Small adenomas, multiple or single, are frequently observed in the kidneys. They are usually subcapsular and present a papillary intracystic structure. These small adenomas arise in sclerotic areas of arteriosclerotic or fibrotic kidneys. A solid type of adenoma which arises from the tubules is also seen commonly, not specifically related to vascular changes. Rarely are the solid adenomas of such dimensions as to be evident clinically. In the latter instance, they are usually mistaken for malignant neoplasms.

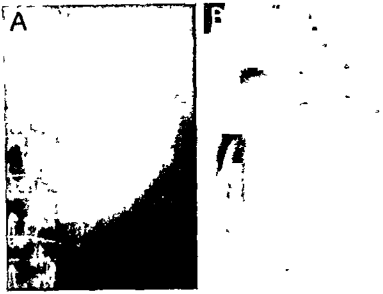

FIG. 1. *A*, Showing hydronephrosis and distortion of pelvis and calyces by tumor mass. *B*, X-ray of surgical specimen. Note how pelvic and calyceal distortion conforms to spherical shape of tumor.

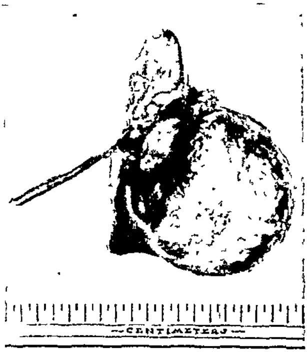

FIG. 2. Gross specimen

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Sturm presented a fairly accurate description of renal adenoma as far back as 1875. Higgins reviewed the literature in 1944 and accumulated a total of 29 cases, 2 of which were discovered accidentally at autopsy. An additional case was reported by Strauss. The case that is herewith presented displayed clinical symptoms which warranted a tentative diagnosis of malignant tumor, but which on section proved to be histologically benign.

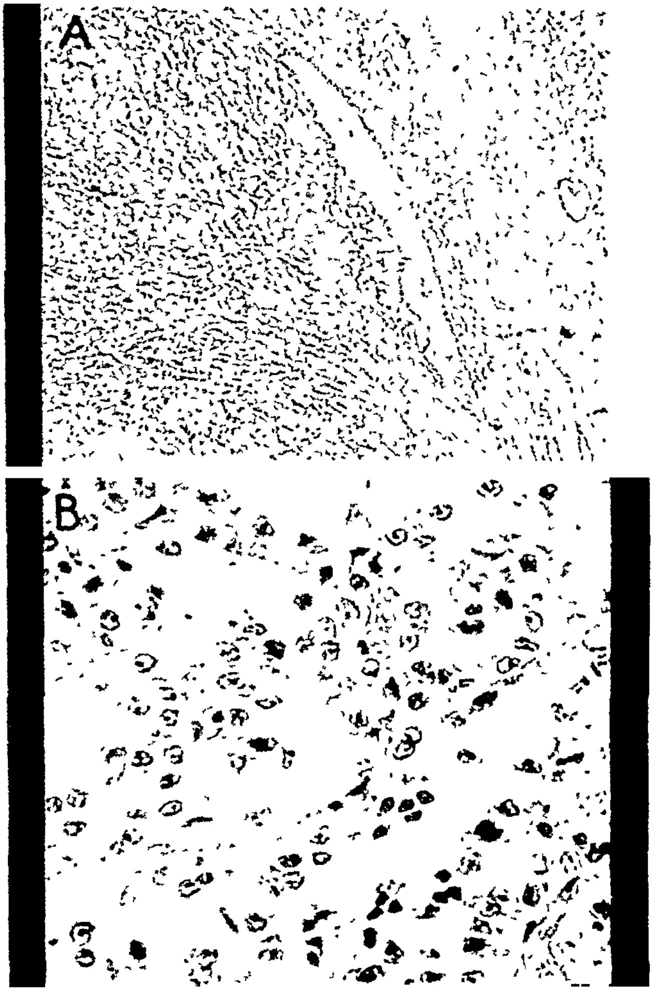

Fig. 3 *A*, Showing demarcation of tumor and compressed renal parenchyma. *B*, Showing benign tubular structure of tumor.

CASE REPORT

A 38 year old white male complained of bloody urine of 2 days' duration. Three weeks prior to admission, the patient noticed simultaneously the presence of a large varicocele and the passage of blood on voiding. The hematuria was total, painless, and persisted for 2 full days. There were no other concurring symptoms. One week prior to hospital admission, however, he noted a dull dragging type of ache localized along the left side of the abdomen.

There was no evident loss of weight The blood pressure was 155/90 The abdomen was negative The liver and the right kidney were not palpable In the left upper quadrant, there was a firm, nontender, rounded mass about the size of a small grapefruit which moved with respiration There was no lymphadenopathy A left varicocele was present The prostate gland was enlarged 1 plus, soft, symmetrical and nontender The seminal vesicles were not palpable

The urinalysis, blood cytology and serology were negative The blood chemistry was normal

Cystoscopy was negative

Intravenous urography revealed good excretion of the dye from both kidneys within 5 minutes The left kidney was enlarged with considerable hydronephrosis of the left renal pelvis (fig 1, *A*) Retrograde pyelography showed no obstruction of either ureter The right calyces and pelvis were normal The left kidney pelvis was dilated The x ray of the chest was negative

The history of hematuria, the presence of a palpable mass in the left upper quadrant, and the finding of hydronephrosis of the left renal pelvis without any ureteral obstruction warranted an exploration of the left kidney, with a tentative diagnosis of hypernephroma At operation, there was a globular mass which formed part of the lower pole of the left kidney

Pathologic description The kidney measured 15 by 12 by 4 cm The capsule stripped with ease, leaving a smooth external surface Section disclosed a dilated pelvis and dilated calyces Attached to the lower pole and apparently arising from the medial surface was a large spherical tumor which measured 11 cm in diameter The tumor was soft in consistency, and on section, displayed a gray, partly hemorrhagic surface See figures 1, *B* and 2 Microscopic examination of the tumor disclosed a discontinuous capsule composed of partially hyalinized fibrous tissue In other sections, the capsule was made up of thin strands of renal interstitial fibrous tissue with numerous compressed blood vessels and tubules The tumor presented a simple structure of relatively mature tubules of the "distal convoluted" type, separated by thin vascularized connective tissue The lining cells were cuboidal, with abundant finely granular cytoplasm and round vesicular nuclei The histologic structure was that of a benign tubule adenoma See figure 3

SUMMARY

Small adenomas of the kidney are common, but large solid adenomas which are clinically evident are rare Such palpable tumors are usually regarded clinically as malignant A case of a single solid tubule adenoma is described which was palpable and produced hematuria

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ADENOCARCINOMA AND TUBERCULOSIS OF THE SAME KIDNEY: REVIEW OF THE LITERATURE AND REPORT OF SEVEN CASES

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A recent case of combined adenocarcinoma (hypernephroma type) and tuberculosis found in the same kidney brings to our attention again the rarity of this lesion. It is of interest to give a brief review of the literature and to report succinctly the 7 cases in which such lesions have been removed surgically at the Mayo Clinic.

Although Albarran and Imbert (1903) were said by Ljunggren to have been the first to produce microscopic proof of the simultaneous occurrence of these two diseases, the credit for early observations on the condition was given by Ljunggren to Chomel (1814) and Rayer (1841). However, microscopic evidence was not presented by the latter two observers.

Keen in 1934 reviewed the literature, and identified a total of 13 cases, to which he added another. This group included 1 case from the group of 7 from the clinic that will be presented herein. This case previously was described by Cooper in 1932. One case of tuberculosis, calculous uropyonephrosis and Grawitz tumor in the same kidney, presented by Lorenzetti in 1930, might be added to Keen's review of the literature, so that there was a total of 14 cases (exclusive of the aforementioned case reported from the Mayo Clinic) until 1934.

A review of the literature reveals that 5 additional cases have been recorded since 1934.

Béla Pitrolffy-Szabó in 1935 reported on a 47 year old woman who had an enlarged right kidney. Tubercle bacilli were excreted during retrograde studies of the flow of urine from the kidney. The kidney was removed and found to contain caseous tubercles in the upper pole and a hypernephroma about 6 cm. in diameter in the lower pole.

De Langre in 1936 presented a case in which tubercle bacilli were isolated from the left kidney of a 60 year old man. Nephrectomy was done, and a hypernephroma was found in the lower pole of the kidney; the remaining portion contained an inflammatory and ulcerative tuberculous process.

Altshteyn in 1936 presented a case in which a 49 year old man had been found, at retrograde pyelography, to have a filling defect in the upper portion of the renal pelvis. The kidney was removed. A carcinoma was seen to be present in the upper pole; miliary tuberculosis was scattered throughout the remaining portion of the kidney. The patient died sometime thereafter, of pulmonary tuberculosis.

Chwalla in 1937 presented a case in which a 67 year old woman was found, at retrograde pyelography, to have a tumor of the kidney. Nephrectomy was done.

A large tumor was found in the upper portion; the tumor microscopically proved to be a hypernephroma. Numerous microscopic tubercles also were found in the surrounding renal tissue.

Alapin in 1936 described the condition of a 43 year old man who was found to have tubercle bacilli on retrograde studies of the flow of urine from the right kidney. Accordingly, nephrectomy on the right was done. Caseous tuberculosis was present in the lower pole of the kidney, and a hypernephroma was found in the upper pole.

To the aforementioned group of 19 cases of combined renal tuberculosis and hypernephroma we wish to add 7 cases.

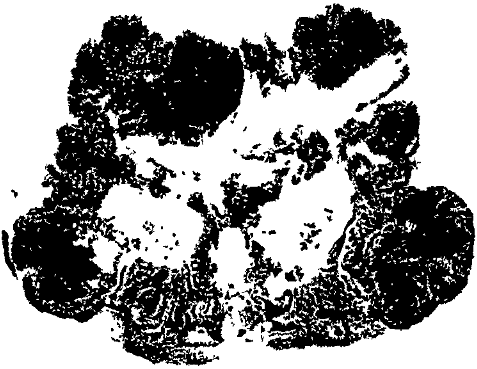

FIG. 1. Case 1. Tumor thrombus and necrotic, caseous tuberculosis

REPORT OF CASES

Case 1. A 38 year old white man registered at the Mayo Clinic for the first time in October 11, 1929. He complained chiefly of urinary frequency, with some degree of dysuria at the end of micturition. Nocturia and a history of pyuria also were reported.

Preoperative studies of the urine revealed erythruria of grade 1 and pyuria of grade 4. Acid-fast bacilli were not found in the urine. An excretory urogram revealed pyonephrosis on the right, thought to be tuberculous in origin. Retrograde studies of the flow of urine were not made, and guinea pigs were not inoculated with specimens of urinary sediment. A roentgenogram of the thorax revealed thickened pleura in a localized area on the right side. Results of other laboratory tests were essentially negative.

Operation was performed on October 22, 1929. The right kidney was found to be about 3 times normal size, forming a pyonephrotic sac. There was much inflammatory reaction about the vascular pedicle. Subcapsular nephrectomy on the right was done.

The kidney weighed 840 gm. A grade 2 adenocarcinoma (hypernephroma) 4 by 2.5 by 2.5 cm. was associated with tuberculous pyonephrosis (figs. 1, and 2 *a* and *b*). Destruction of about 70 per cent of the substance of the kidney had occurred.

The patient returned to the clinic in 1938, complaining of epigastric pain. A mass was found in the right upper quadrant of the abdomen and was diagnosed as probably being a malignant process. Palliative roentgen-ray therapy was commenced at the clinic and the patient continued to receive it at home. A report that death with metastasis of a malignant process to the liver had occurred on July 16, 1939, was received subsequently.

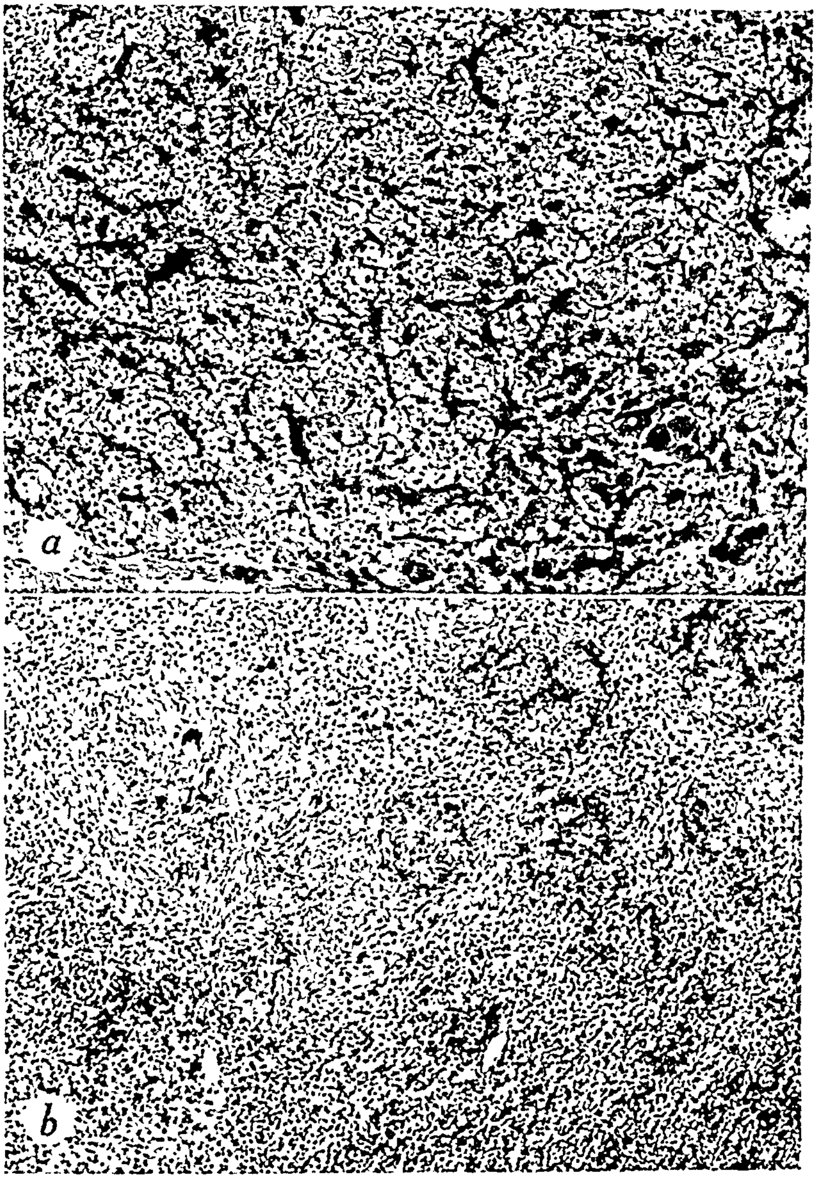

FIG. 2. Case 1. *a*, Section of hypernephroma excised (hematoxylin and eosin ×70); *b*, section showing renal tuberculosis (hematoxylin and eosin ×70).

Case 2. A white man 44 years old registered at the clinic for the first time on February 12, 1930 He complained chiefly of nocturia accompanied by pain in the back Hematuria and pyuria had been noted during examination elsewhere.

Preoperative studies of the urine revealed both pyuria and erythruria Excretory urograms were not particularly informative Retrograde studies of the flow of urine from the kidneys revealed evidence of probable renal tuberculosis on the right A specimen of urine obtained by catheter from that side gave positive results for tuberculosis when a guinea pig was inoculated with the sediment The left kidney was normal Results of a roentgenogram of the thorax and of other laboratory procedures were within normal limits

An operation was performed on January 5, 1931 Through a right posterolumbar incision, the kidney appeared grossly normal externally Hence, the left kidney was explored through an incision in the peritoneum A retrocecal appendix was found and removed, after which the peritoneum was closed and the right kidney was removed This kidney weighed 145 gm Tuberculosis was found to be limited mostly to the renal papillae, 5 per cent of the substance of the kidney had been destroyed A grade 1 adenocarcinoma (hypernephroma type) 3 cm in diameter was found, in addition to the tuberculosis

A communication was received from this patient in 1939, 8 years postoperatively, in which he said he was in fairly good health and that his only complaint was that of slight backache

Case 3. A white man 44 years old registered at the clinic on June 19, 1933 He complained chiefly of hematuria, frequency of urination and slight dysuria He said he had received a severe injury in the form of a blow to the region of the left kidney 1 month prior to the onset of his symptoms Examination elsewhere had revealed pyuria in addition to hematuria

Urinalysis revealed erythruria of grade 1 and pyuria of grade 4 A pyelogram disclosed irregular dilatation of calyces of grade 3 and ureterectasis of grade 3 on the left Results of culture of the urine from that side were negative, but inoculation of a guinea pig with urinary sediment from the left produced the lesions of tuberculosis

A roentgenogram of the thorax showed extensive tuberculosis of the upper lobes of both lungs, probably inactive at that time Results of other laboratory examinations were essentially negative

On July 11, 1933, an operation was performed by Dr Walters Through a left posterolateral incision the kidney was noted to be considerably enlarged, with a tumor the size of a hen's egg in the lower pole (fig 3) Marked ureteritis, with a thickened, edematous, pipestem ureter enlarged about twice normal size, was seen The kidney was removed and partial ureterectomy was done

The kidney weighed 575 gm A hypernephroma 3 by 3 5 cm was found in the lower pole (fig 4 *a*) There was evidence of diffuse tuberculosis of the kidney and pelvis (fig 4 *b*), with destruction of 65 per cent of the substance of the kidney

Subsequently, tuberculosis of the remaining kidney developed This was followed by uremia and death of the patient on May 15, 1934 health. In a communication dated August 30, 1946, he said his condition was good.

Case 5. A white woman 50 years old registered at the clinic for the first time on January 2, 1942. She complained chiefly of discomfort in the area of the left flank, and loss of weight and strength over a period of 6 months. During the previous 10 days she had noted some degree of hematuria.

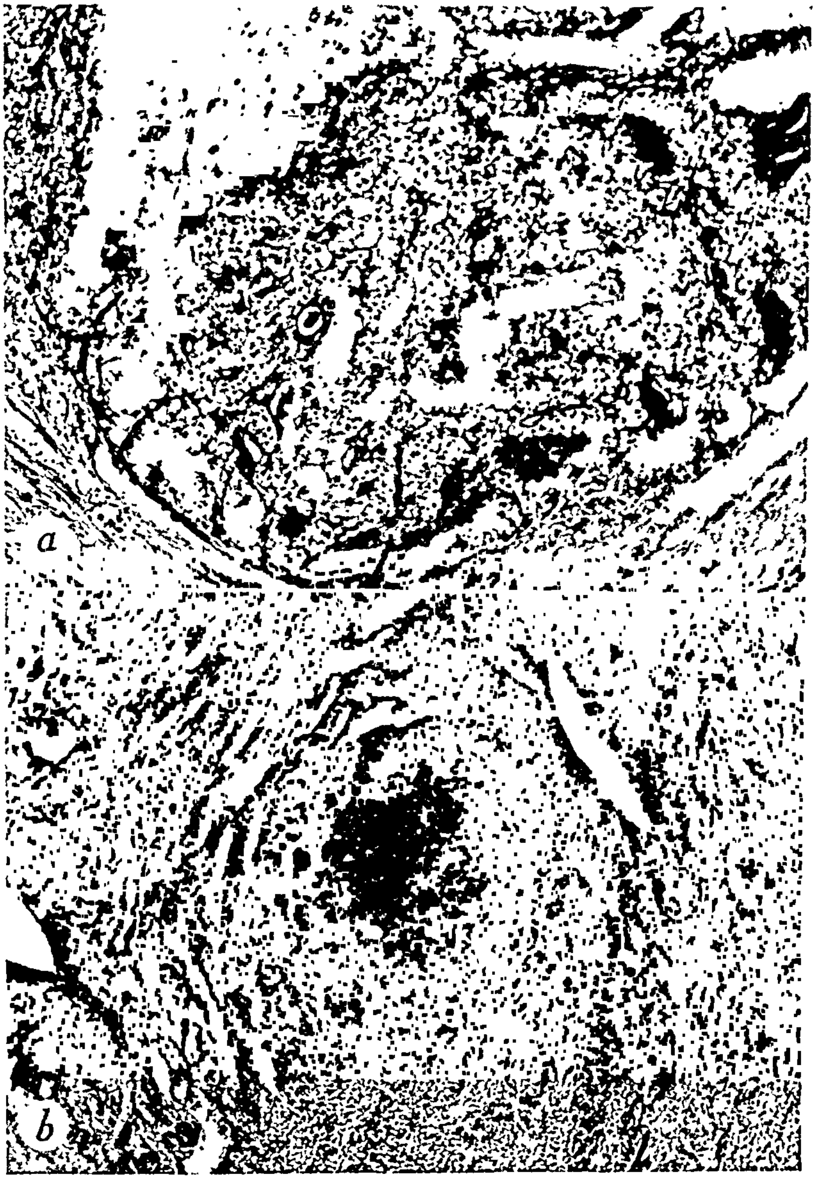

FIG. 5. Case 5. *a*, Section of hypernephroma (grade 1 adenocarcinoma) of left kidney (hematoxylin and eosin ×70); *b*, section of tuberculosis in upper pole of left kidney (hematoxylin and eosin ×70).

Studies of the urine revealed an occasional erythrocyte and pyuria of grade 4. An excretory urogram disclosed a soft-tissue mass in the left renal area. Results of a roentgenogram of the thorax and of other studies were essentially negative.

On January 5, 1942 an operation was performed by Dr. Walters. Through a left posterolumbar incision, a well encapsulated mass, approximately 18 by 10 cm, was found The pedicle of the mass was triply ligated, and the kidney was removed in the usual manner Examination of the kidney revealed a grade 1 adenocarcinoma (hypernephroma type) 16 by 9 by 9 cm (fig 5 *a*) Ulceration of the renal pelvis and thrombosis of the renal vein were found Tuberculosis was noted to have invaded the remaining portion of the kidney (upper pole) (fig 5 *b*) The weight of the kidney was 1,090 gm

The condition of the patient followed a gradually downhill course Death occurred 14 or 15 months later

Case 6 A white man 44 years old registered at the clinic for the first time on July 29, 1942 The diagnosis of a functionless right kidney was made, the possibility that a horseshoe kidney might be present was considered The question of surgical operation was raised at that time, but the patient elected to return to his home

He returned on January 20, 1944 At that time he said that in June, 1943, he had had an episode of acute pain in the back, fever and anuria This had been relieved only when his local physician passed a ureteral catheter, so that drainage of urine followed The pain returned when the catheter was removed It was necessary to pass the catheter again, and it was left in position for 5 days The patient had had no difficulty since

Urinalysis disclosed pyuria of grade 2 (40 cells per field with the high power objective) An excretory urogram revealed a functionless half of a horseshoe right kidney which was filled with large calcareous masses Retrograde studies of the flow of urine from the left kidney revealed no evidence of infection on that side, but similar studies could not be carried out on the right, since no meatus could be located Results of a roentgenogram of the thorax and of other studies were essentially normal

An operation was performed on January 25, 1944, at which time semihorseshoe type kidneys were found which were connected by a fibrous band This band was divided, and the right kidney was removed

The excised kidney weighed 76 gm Marked cavitation caused by caseous tuberculosis (fig 6 *a*), with destruction of nearly all the substance of the kidney, was found A grade 1 adenocarcinoma 4 mm in diameter was noted in one portion of the cortex (fig 6 *b*)

The patient advised us on August 26, 1946 that there had been no recurrence of symptoms, and that he had gained weight and was feeling well generally

Case 7 A white man 63 years old registered at the clinic for the first time on February 28, 1946 His history indicated that he had been well until November 1944, at which time he had noted fever, malaise, anorexia and loss of weight His temperature, for about a month, had increased daily to 100 5° F (38 1° C), and thereafter it had increased daily to 99° or 99 5° F (37 2° to 37 5° C) In the summer of 1945 an examination performed elsewhere showed a mass to be present in the left upper abdominal quadrant This mass was thought to be the spleen, and treatments directed at malaria and undulant fever had been carried out

When the patient registered here for the first time in February 1946, a huge mass in the left upper abdominal quadrant was noted on examination. It seemed to be cystic, extended to the midline and down as low as the umbilicus, pushing the ribs on the left side outward. No bruit was heard, and the liver and right kidney were not palpable. The remainder of the general physical examination was essentially without significance.

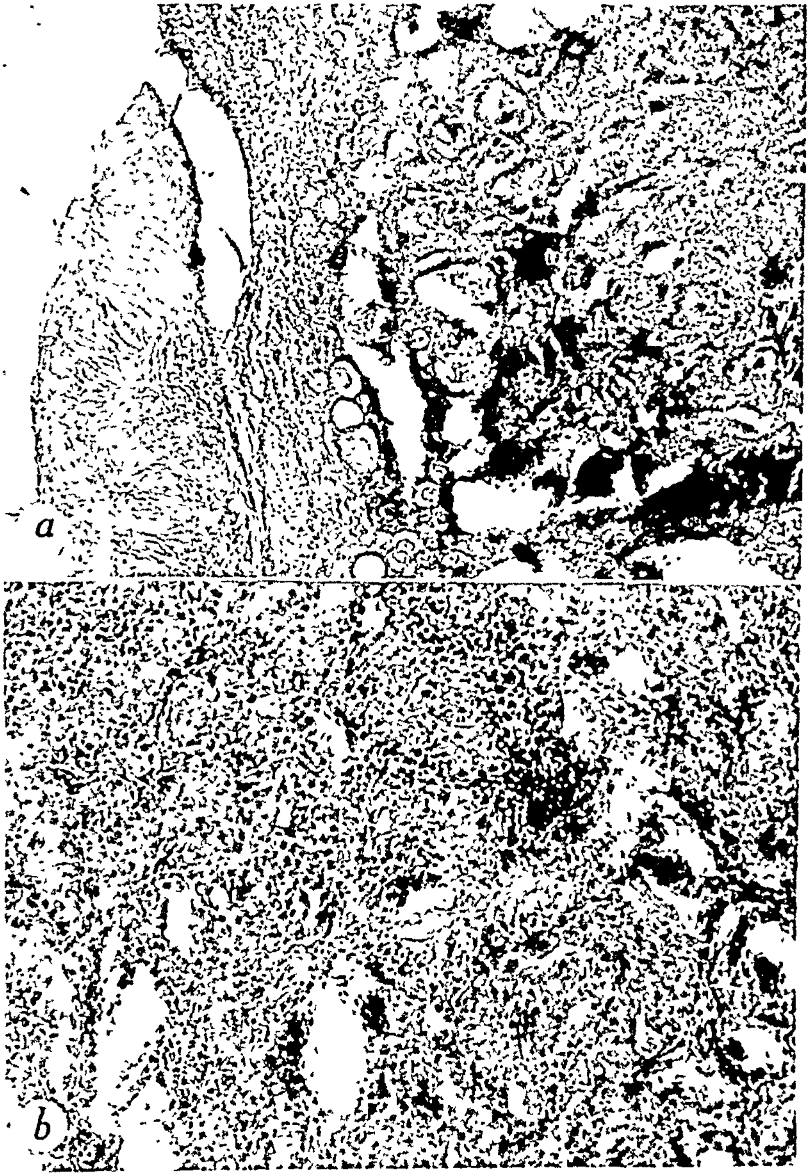

FIG. 6. Case 6. *a*, Section of hypernephroma and old tuberculous sac near by (hematoxylin and eosin ×45); *b*, section of hypernephroma (grade 1 adenocarcinoma), area of tissue shown in *a*, but at higher magnification (hematoxylin and eosin ×145).

Laboratory studies revealed the content of hemoglobin to be 12.7 gm. per 100 cc of blood; erythrocytes numbered 4,280,000 and leukocytes 7,100 per cubic millimeter of blood. The sedimentation rate was 65 mm. in 1 hour (Westergren). The value for urea was 44 mg. per 100 cc of blood; for bilirubin, direct, 0, indirect, 0.5 mg. per 100 cc of serum; for amylase, 50 units. A test of hepatic function revealed no retention of dye and results of a test for agglutination of the micro-organisms of brucellosis were positive only at a concentration of 1:640 or less. Roentgenologic examination of the thorax disclosed no abnormality. Urinalysis revealed a specific gravity of 1.017, an alkaline reaction, no albumin or sugar and pyuria of grade 1 (6 cells per field with the high power objective).

A plain roentgenogram of the abdomen disclosed a large soft-tissue mass in the position described previously herein. An excretory urogram did not produce visualization on the left, but normal function and characteristics were demonstrated on the right side.

Retrograde roentgenologic studies were made which showed an elongation of the renal pelvis and calyces on the left. The tips of the calyces appeared to be normal. Cystoscopic examination during the course of the retrograde studies disclosed a small collar type of prostatic hypertrophy, but no residual urine. Trabeculation of the bladder was not seen. Gram's staining procedure of urine from the bladder and from the left kidney gave negative results.

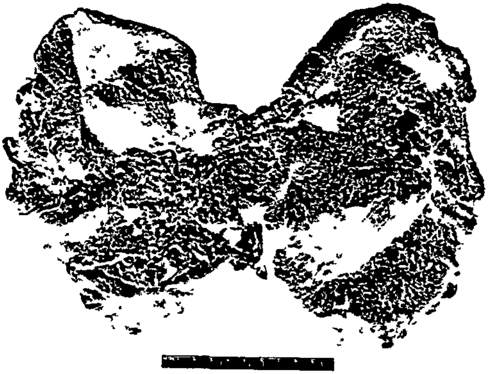

FIG. 7. Case 7. Caseous and necrotic tuberculous sac, with area of malignancy, of cystlike tumor removed with left kidney.

The opinion was that the tumor was a large hypernephroma. Operation was advised. On March 13, 1946, the kidney was surgically explored by one of us (Walters) through a left posterolateral incision. The tumor mass as exposed appeared to be about 24 by 16 by 16 cm. It had the thick-walled, cystic appearance of a pancreatic cyst. A trocar was inserted into the cystic mass, and approximately 2,500 cc of thick yellow fluid was drained. In the fluid cholesterin-like crystals could be seen reflecting the light. Within the cystic cavity were 2 or 3 free masses, each about 5 by 3.5 cm., of degenerating lemon-yellow material.

After removal of the fluid from the cystic cavity it was apparent that the tumor was attached to the lower pole of the kidney. The kidney and tumor were removed, the renal pedicle was ligated and the perirenal fossa was washed out with water. Alcohol was then applied to the perirenal area to fix or destroy any tumor cells which might have escaped excision.

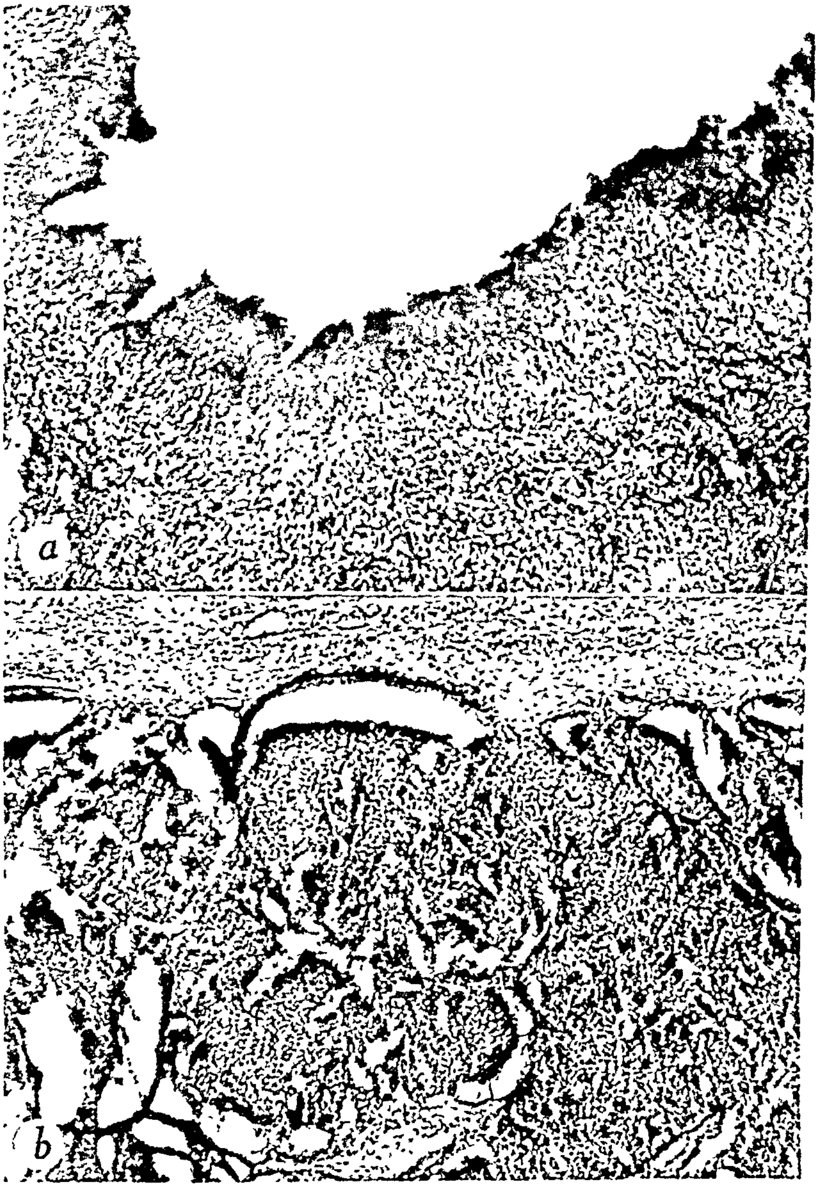

FIG. 8. Case 7. *a*, Section of caseous tuberculous sac of tumor removed with left kidney (hematoxylin and eosin ×70); *b*, section of hypernephroma (grade 2 adenocarcinoma) of left kidney (hematoxylin and eosin ×70).

The empty sac of the tumor weighed 625 gm. (fig. 7). The tumor consisted of a chronic caseous tuberculous process, with cavitation (fig. 8, *a*), intimately associated with a grade 2 adenocarcinoma (hypernephroma type) (fig. 8, *b*). Results of culture of material taken from the tumor were reported as "no growth of organisms." Culture to produce Mycobacterium tuberculosis hominis was not carried out.

Subsequently, the patient in a letter dated August 27, 1946, said he had regained weight to about his normal figure, and that he was feeling well Results of a roentgenologic examination done by his local physician were reported as normal An indirect communication received 7 months after the operation indicated that he was in good health

COMMENT

As can be ascertained from a study of the preceding reports of cases, all the patients were male except the one in case 5 The ages varied from 38 to 63 years, with an average of 50 1 years Preoperatively, the condition of 4 of the 7 patients was thought to be tuberculous In 2 of these cases urinary sediment gave positive results when guinea pigs were inoculated with it In the third case, definite pyonephrosis on the right, probably tuberculous, was found, but guinea pigs were not inoculated with urinary sediment in this case In the fourth case a presumptive diagnosis of renal tuberculosis was made on the basis of the excretory urogram, but it was impossible to catheterize the ureter on the affected side for studies of the urine and to obtain material for the inoculation of animals

In 2 of the cases excretory urography demonstrated large soft tissue masses, and hence, in the presence of other substantiating observations, the condition in these cases was diagnosed as "renal neoplasm"

In 1 case a horseshoe kidney was found in which the right half appeared functionless and was filled with large stones It is of interest, in relation to this case, to note that Braasch has commented on the frequency with which hypernephromas may undergo calcification and on the fact that they may thus be confused with calcified tuberculous lesions in the course of diagnostic procedures

It also may be noted, in respect to these 7 cases, that in the cases in which the diagnosis was tuberculosis, 2 patients had evidences of previous pulmonary involvement and that the thoraces of the remaining 2 were normal roentgenologically In addition, 1 of the 2 patients who had evidence of previous pulmonary tuberculosis also had a history of previous tuberculous involvement of both knees The latter condition apparently had cleared entirely several years prior to the appearance of any renal symptoms Results of roentgenologic examination of the thorax were negative in the 3 cases in which the diagnosis had been other than tuberculosis

Surgical considerations and removal of these lesions present primarily the same problems as those encountered in nephrectomy for hypernephroma or for tuberculosis, depending on which disease the combination found in this series most nearly resembled The incisions used were posterolumbar, because it has been the consensus at the Mayo Clinic that most tumors of the kidney are as accessible by this approach as by the transperitoneal approach advocated by some authors for the removal of large renal tumors The adequacy of the posterolumbar approach is illustrated by the relative ease with which the large tumor in case 7 was removed This tumor was a cystic mass 24 by 16 by 16 cm from which some 2,500 cc of fluid was aspirated by trocar

Nephrectomy in all cases was carried out in the usual manner, the attempt being made to isolate and clamp the renal vein as early in the operative procedure as possible. When the lesion resembled a frankly tuberculous condition and there was concomitant ureteritis, partial ureterectomy also was done.

Pathologically, the malignant processes were mostly of low grade (Broders method), with a preponderance of grade 1 lesions. This range of grade is in keeping with the observations of McDonald and Priestley, who showed that the majority of hypernephromas removed at the Mayo Clinic are of the lower grades—1 and 2—based on the Broders method of classification.

The size of the tumors varied greatly from the smallest discrete hypernephroid lesion of 3 mm. in case 4 to the largest tumor measuring 24 by 16 by 16 cm. in case 7, in which the malignant process and the tuberculosis were intermingled indiscriminately.

It is also of interest to observe that most of these lesions contained discrete areas of hypernephroma in a tuberculous kidney or small portions of tuberculosis in a kidney mass composed chiefly of neoplastic tissue (cases 1 through 6), whereas only in case 7 was there apparent, grossly, an intermingling of tuberculosis and carcinoma.

The length of survival of the patients after operation is in close agreement with the general prognostic tables suggested by McDonald and Priestley in respect to hypernephromas. Four of the patients had kidneys or tumors weighing more than 500 gm. One of these 4 patients (case 5) had concomitant involvement of the renal vein. Two of these 4 patients had lived more than a year after operation, at the time of this report, and 1 patient operated on recently (case 7) had been in good health 7 months since operation, according to an indirect communication. One patient died about a year after operation, of uremia after the development of tuberculosis in the other kidney (case 3). Three patients had kidneys or tumors weighing less than 500 gm. These cases, all without involvement of the renal vein, were alive 9, 5 and 2½ years postoperatively when last heard from (cases 2, 4 and 6).

On the basis of follow-up studies of these patients, it is at least suggestive that the prognosis in this combination of diseases probably is no better, and actually may be worse, than in the case of the single disease, hypernephroma.

SUMMARY

A review of the literature, and especially the isolated reports of cases presented since the last general review of the literature on the subject, together with a summary of 7 cases of combined tuberculosis and hypernephroma of the same kidney, has been presented.

It is noted that the diagnosis is directly related to that portion of the combined disease which predominates. In no recorded instance has the complete diagnosis been made preoperatively.

Prognosis probably is no better for the combined disease than it is for hypernephroma alone.

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SURGICAL ASPECTS OF BILATERAL FAMILIAL PHEOCHROMOCYTOMA[1]

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The clinical syndrome of paroxysmal hypertension has always been a fascinating diagnostic problem, and its association with tumors arising from the medullary portion of the adrenal gland—pheochromocytoma or paraganglioma—has been recorded many times in the literature. During the past year 2 cases of this syndrome have been studied and operated upon at the Johns Hopkins Hospital. These cases presented such unusual features that a report on the surgical aspects of the problem should be recorded. The diagnostic studies were carried out by Drs. Evan Calkins and John E. Howard of the Department of Medicine who have also made an extensive study of the available world literature on the subject. With their permission I shall quote extensively from their article with a discussion of some of the surgical problems which arose in the management of these cases.

First of all, in the study of these individuals was the interesting fact that they were blood relations—aunt (R. L.) and niece (M. M.)— and that the latter's mother and the former's sister had died at the age of 28 from hypertension, which had manifested itself by symptoms very similar to those presented by both of our patients. A second feature of extreme interest is the fact that both patients suffered from bilateral tumors which were successfully removed by surgical operation, and in 1 case (M. M.) 3 such tumors—one recurrent after previous operation—were excised. These are the first cases in the literature from which bilateral tumors have been successfully removed, and M. M., from whom three pheochromocytomata have been excised, will probably remain unique.

Calkins and Howard found reports of 176 pheochromocytomata in the world's literature, "but only 47 of them were proven to be endocrinologically active by cessation of symptoms following surgical removal." They also found "15 cases of bilateral pheochromocytomata in which the tumors were located in or near the adrenal glands, and 2 cases each with tumors arising in Zuckerkandl's body and the retroperitoneal ganglia.

"It should be emphasized that no surgical attempt was made to remove the tumors in any of these cases. There is no proof, therefore, that the pheochromocytomata were actively secretory and responsible for any of the patient's symptoms, though in many instances it seems altogether likely. Insofar as we are aware, the patients here reported are the first from whom more than one pheochromocytoma has been removed. MacKenzie, in discussing a paper by Hyman and Mencher, mentions a patient of his own whose paroxysmal hypertension disappeared after removal of a tumor. Four and a half years later the symptoms recurred. Though careful exploration of both adrenal areas failed to reveal a tumor, MacKenzie was of the opinion that another pheochromocytoma existed somewhere."

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

Malignant tumors arising from the medullary portion of the adrenal gland have been reported, and it is an important fact that of the 17 cases of bilateral pheochromocytomata which Calkins and Howard found recorded in the literature, 5 were found to be malignant, and in none of these cases were symptoms of paroxysmal hypertension present. In 15 of the cases of multiple tumors, pheochromocytomata were located in or near the adrenal glands, and in 7 the patients were known to have suffered from constant hypertension. In these 7 cases the tumors were benign. Up to the present no case of malignant tumor associated with the clinical syndrome of paroxysmal hypertension has been reported, but McKenna and Hines in 1935 reported a case with precordial palpitation and blood pressures ranging from 160–190 from which a tumor, microscopically malignant, was removed. The patient died 2 years later of metastases.

Of the 10 cases of benign bilateral pheochromocytomata reported, 7 contained information on blood pressure, and all these patients had hypertension. McGavack records his impression that patients with malignant tumors have normal blood pressure.

PATHOLOGY

Pheochromocytomata are usually well encapsulated though the capsule may be thin and delicate. On section the tumor is soft and has a characteristic reddish brown appearance. In the benign types areas of hemorrhage, necrosis and calcification may be present, but are more frequently seen when malignant changes have occurred. The adrenal gland is often compressed and flattened, especially in the larger tumors, and may be partially incorporated in, or densely adherent to the capsule of the tumor.

Microscopically many large anastomosing venules and sinusoids are present, especially in the central portion of the tumor. The tumor cells are arranged in fairly large groups and cords of irregular shape, between which there are delicate connective tissue septa with capillaries.

The individual cells are rather large and polygonal, and do not vary much in size or appearance. The cytoplasm is coarse and granular and often contains basophilic and eosinophilic granules. The pheochrome properties of the cells are evidenced by their hazy brown color. The nuclei are usually rounded or oval and most are hyperchromatic, some with large nucleoli. In general the tumor cells more closely resemble ganglion cells than the chromaffin cells of the normal adrenal medulla.

SYMPTOMS

In the typical case of paroxysmal hypertension the patient suffers from sudden episodes, usually characterized by severe generalized headache associated with blanching, particularly around the mouth, and cold extremities followed by generalized flushing and a sensation of warmth. The characteristic diagnostic feature is a rapid rise of blood pressure. Before the episode the pressure usually is at normal levels, but with the onset of the attack both systolic and diastolic rise rapidly within a few minutes, often to astonishingly high levels. As the attack diminishes in intensity, the pressure returns to its previous normal level. The episodes usually last for 5 to 15 minutes, are often accompanied by nausea and vomiting and fainting spells with momentary unconsciousness. During the episode there is a feeling of marked anxiety and apprehension, and following it marked lassitude and complete exhaustion. With the course of the disease the episodes become more frequent and more severe, and death may occur in one of the crises, either from acute myocardial failure or from a cerebral accident. The episodes may be brought on by lying in a certain position, particularly on the side in which the tumor is located, by straining at stool and by emotional crises, such as anger or sudden fear.

DIAGNOSIS

When a patient presents the above symptom complex, the probability of the presence of a pheochromocytoma should be strongly suspected. These tumors may also be found in cases of sustained hypertension. Smithwick reports 2 cases in which, in the course of operative exposure for the purpose of sympathetic ganglionectomy for essential hypertension, pheochromocytomata were found, after the removal of which the blood pressure returned to normal limits. The diagnostic difficulties in such cases are obvious, and as yet a correct preoperative diagnosis has not yet been reported in a case of sustained hypertension due to the presence of a pheochromocytoma.

When the clinical picture is suggestive of the presence of a pheochromocytoma, radiographic studies should first be carried out. In the flat film and intravenous urogram in some cases a soft tissue shadow may be visualized in the adrenal area, and the corresponding kidney may be displaced downward, but in many cases, particularly when a small tumor is present, no significant information can be obtained. If satisfactory intravenous urograms are obtained, no further information of value can be expected from retrograde pyelography.

Perirenal air or oxygen insufflation has been recommended as a valuable diagnostic procedure, particularly by Cahill. That this technique is of great value in many cases is without question, but often the results from a diagnostic standpoint are equivocal and great difficulty in the correct interpretation of the films may exist. Furthermore, the literature on this subject contains reports of sudden death from air embolism, probably due, it is true, to faulty technique. Nevertheless, the possibility of a tragedy resulting from what should be a minor diagnostic procedure cannot be ignored with temerity. In the 2 cases which are the subject of this report, the particular side on which the tumor was located was inferred from the law of probability in case 1 because at previous operation a portion of the capsule could not be removed, and it was therefore considered that recurrence of the original tumor was the most probable cause of the recrudescence of her symptoms. It is quite possible, however, that if perirenal insufflation had been carried out and clear-cut films obtained, the presence of bilateral tumors—one recurrent postoperatively—could have been recognized.

In case 2 the tumor in its capsule, together with the kidney, had been removed so that a tumor of the opposite adrenal was considered the most likely possibility.

In 1945 Roth and Kvale described a tentative test for pheochromocytoma. These observers found that by an intravenous injection of 0.05 mg. histamine base in 3 patients with pheochromocytoma the blood pressure "rose approximately 100 mm. more than the elevation obtained by the cold pressor test and was accompanied by the characteristic symptoms of a typical spontaneous attack."

Calkins and Howard state that "our experience with the use of the Roth-Kvale test coincides closely with theirs. In our patients the injection of histamine produced an abrupt rise in blood pressure, which dwarfed that which accompanied the cold pressor test. The drug seemingly induced episodes which were in all respects identical with spontaneous attacks. The test appears to have a two-fold value, first as a method of producing attacks at will for study, and, second, as an indication of the presence of pheochromocytoma. In the patients here reported, so long as the test remained positive, it was possible to find and remove more tumors. Conversely, so far as known, no pheochromocytomata have been found in patients in whom the test was negative."

From the foregoing the great value of this simple test is obvious. In our two patients severe attacks of paroxysmal hypertension were induced by the injection of histamine, but these attacks were no more severe than some of the spontaneous episodes. The great value of the test as a diagnostic procedure would certainly seem to outweigh any possible dangers.

SURGICAL PROBLEMS

When a diagnosis of probable pheochromocytoma has been tentatively made, and the side on which the tumor is located has been determined as accurately as possible in accordance with the foregoing, it is obvious that an attempt to remove the tumor surgically should be undertaken as soon as possible in order to spare the patient from the hypertensive crises, any one of which might conceivably terminate in a fatal outcome. These tumors are usually well encapsulated, but the capsule is often quite thin and may tear easily so that great care should be taken during the surgical procedure to avoid this accident. If a previous operation has been performed, the resulting scar tissue may greatly complicate the enucleation and enhance the danger of tearing the capsule.

The adrenal gland is usually found flattened out, compressed and either adherent to, or partially incorporated in the capsule. In many cases excision of the entire adrenal has been carried out to ensure complete removal of the tumor without injury to its capsule. The possibility that the adrenal on the opposite side may be absent or if present that its function might be insufficient to sustain life cannot be ignored so that, if technically possible, as much as possible of the adrenal tissue must be conserved. In Case 2 we were faced with the fact that the entire left adrenal gland with the tumor and the kidney had been removed at the first operation. On exposure of the tumor on the right side about two-thirds of the adrenal gland was found so intimately incorporated in the capsule of the tumor that to preserve the gland in its entirety, it would have been necessary to leave behind some of the capsule of the tumor. However, it was possible to separate about one-third of the adrenal with intact blood supply from the tumor. A clamp was placed across this portion of the adrenal as close to the capsule of the tumor as possible, and the latter was then excised leaving behind about one-third of the adrenal, normal in appearance and with intact blood supply. In spite of the obvious hazard that this small remaining portion of the gland would be inadequate to support life the clinical picture and the findings at operation were such that this course was deemed justifiable.

The blood supply of these tumors comes mostly from the adrenal gland itself, though some operators have described a vascular pedicle arising independently from the great vessels above the origin of the main vessels supplying the adrenal. In our own three operative experiences no such definite pedicle was encountered, and hemorrhage was controlled by clamping individual vessels as they were encountered in the enucleation.

The choice of surgical approach is most important. It is axiomatic, of course, that the exposure must be adequate to enucleate the tumor in its capsule in such a manner that the blood supply will be under direct vision so that its control can be assured. In our three operations the lumbar approach was chosen in each case, and from the previous operative procedures we inferred according to the law of probability the side on which the tumor was located. It must be admitted, however, that in case 1 the possibility of a tumor on the unoperated side had not been sufficiently considered at the first operation.

To ensure adequate exposure the twelfth and eleventh ribs were resected at each operation. By this technique in each instance an excellent exposure of the whole tumor was obtained so that complete removal of each tumor was possible and the blood supply satisfactorily controlled. It was felt in each instance that without resection of the last two ribs complete removal of the tumor would have been impossible or at least extremely hazardous. It will be noted, however, that in each operation, either in the course of the rib resection or in the actual enucleation of the tumor, the pleura was opened. In spite of prompt closure of these accidental injuries, pneumothorax was a disturbing postoperative complication. Fortunately prompt and efficient medical care was available so that these patients were carried through their complications without serious difficulty.

Injury to the pleura might conceivably be avoided by more meticulous operative technique, but this accident must be considered in all operations for the removal of adrenal tumor through a lumbar exposure. In a review of the literature, one is struck by the high incidence of pleural injury by surgeons using a lumbar incision.

In recent years the writer has been impressed with the excellent exposure afforded by the transverse abdominal incision in which the rectus fascia and both recti muscles are completely cut across. This operative approach has been found most adequate for such procedures as simultaneous bilateral ureterosigmoidostomy. The satisfactory healing which occurs without postoperative hernia has been most striking, and in cases of ureterosigmoidostomy we have no hesitation, when the first incision has healed, in making a second, lower transverse incision for cystectomy in cases of extensive malignant disease of the bladder.

On numerous occasions the exposure of both adrenals, which can be obtained by an upper abdominal transverse incision, has been observed in the course of operations on upper abdominal viscera by general surgeons. Although I have had no personal experience with this approach for the removal of adrenal tumors, the exposure has seemed completely adequate for this procedure. This incision in the case of suspected pheocyromocytoma would make perirenal insufflation entirely unnecessary, and if a tumor should be found the surgeon would have the additional comfort of a complete visualization of the opposite side, and thus be able to assure himself as to the condition of the adrenal gland on that side in case the situation made necessary the removal of the entire adrenal on the side where the tumor was located.

Biskind, Meyer and Beadner (1941) collected 29 operations for the removal of pheochromocytoma with 4 operative deaths, and 1 death 30 days later from pneumonia. In 12 cases the transperitoneal approach was used. In 8 of these cases severe shock was recorded, and 3 patients died as a result of the operation, and one, 30 days later from pneumonia. In 4 cases there was no shock at the end of operation, but one developed pneumonia subsequently with wound infection, but recovered.

We were able to find 11 cases, including our own 3 operations, in which the lumbar approach was used. In 5 of these no shock occurred at operation, although in one pneumonia subsequently developed. In 2 cases slight shock occurred, and in 4 cases severe shock, but there were no operative deaths. Although this series is too small for any accurate comparison of the operative approach, the lack of mortality and the fewer cases of severe shock when the lumbar approach was used is significant. This might be explained by the more adequate exposure of the tumor, especially when the eleventh and twelfth ribs are resected, and hence more accurate control of hemorrhage. The frequency with which the pleura is injured in the lumbar approach, however, cannot be disregarded. One of the great advantages of the transperitoneal approach, however, lies in the fact that both of the adrenal glands can be exposed.

CASE REPORTS

Case 1. M. M. (No. 382786), a 22 year old white female, entered the Johns Hopkins Hospital on April 19, 1946. She complained of recurrence of symptoms which had been relieved for a 9 months' period by an operation performed 4 years previously at another hospital. Her mother had died with hypertension at the age of 28, having experienced symptoms quite similar to those of which the patient complained. M. M.'s past history included diphtheria, scarlet fever, ruptured appendix and a dislocated hip, all prior to adolescence. Six months before the onset of her present complaints there had been an illness of

2 weeks' duration, with headache and stiff neck, which she was told was poliomyelitis. There was apparently complete recovery. Menstrual periods had always been regular and the flow normal.

Four years before our observation began, the patient was seized suddenly, while in bed, with a violent generalized headache which lasted only 10 minutes. During the ensuing 3 months similar attacks recurred at approximately biweekly intervals. These episodes were accompanied by blanching and coldness of the extremities and were followed by flushing and a sensation of warmth, without conspicuous sweating. Because of these symptoms, she entered a hospital in New York where an operation was performed with removal of a pheochromocytoma from the left adrenal region. Studies performed and the procedures carried out at that time were fully reported by Hyman and Mencher. The authors were aware that, at operation, the posterior layer of the capsule of the tumor was left in situ, because it was adherent to the surrounding structures.

Following operation the patient had no more attacks for a period of 9 months, after which time the attacks recurred and she began to experience "brief periods of over-fatigue, complete lassitude, tremors, palpitations and alternate blanches and flushes. At first these spells were infrequent, but more recently have been daily occurrences. Within the past month I have had several headaches similar to those in the preoperative period, together with fainting spells and nausea. I am unable to feel completely healthy for even one entire day."

At the time of admission the attacks were occurring several times a day. They commenced apparently spontaneously, although they were especially apt to occur when the patient was at stool or lying in bed on her left side. Heralded by severe generalized headache, they were climaxed by marked blanching and nausea and sometimes vomiting. Occasionally the patient became momentarily unconscious. After about 3 minutes she experienced great warmth, sweated and was left exhausted, the whole episode lasting about 5 minutes.

Physical examination in a resting state revealed a healthy appearing girl of 22. The skin was warm and slightly moist. Pupils were normal, and there were no visible abnormalities in the fundal vessels. The thyroid was diffusely and symmetrically enlarged to about twice average size. Neither thrill nor bruit was present. Heart rhythm was regular, rate slightly rapid. Although the apical impulse was accentuated, there were no evidences of cardiac enlargement. No significant murmurs were heard. Blood pressure was 120/80. The rest of the physical examination was normal.

During attacks she became markedly pale, especially in the extremities and around the mouth. "Goose pimples" might be apparent. An expression of great anxiety appeared, and on occasions she vomited. The blood pressure reached a maximum oı approximately 200/150, but neither the cardiac nor the respiratory rate was much affected. Following the climax, she would become violently flushed, perspire freely and sink exhausted to the bed. The blood pressure did not return to normal for about 10 minutes.

On plain x-ray film the outline of the right kidney was clearly seen, normal in size and position; no suspicious shadows in kidney or ureter, contour smooth.

No suggestion of soft tissue mass was seen above the kidney. A portion of the twelfth and eleventh ribs on the left side had been resected. The outline of the kidney was clearly seen, normal in size and position; contour smooth. No suspicious shadows were seen in kidney and ureter. Above the kidney, beneath the eleventh rib, there was a suggestion of a soft tissue mass, measuring about 4 by 2 cm.

The intravenous urogram showed good excretion of dye in both kidneys. In the 15 minute film the pelvis of the right kidney was well filled, no dilatation, distortion, filling defect or obstruction at the ureteroplevic junction. The calyces were clearly defined, cup-shaped and showed no distortion. The pelvis of the left kidney was well filled, no dilatation, distortion, filling defect or obstruction at ureteropelvic junction. The calyces were clearly defined, cup-shaped and showed no distortion.

The complete laboratory data and special studies are given in full in Calkins and Howard's report, so that only the significant findings and tests will be briefly described here. The cold pressor test produced a rise in blood pressure from 125/70 to 140/100 without symptoms. When 0.05 mg. histamine base in 1 cc normal saline were rapidly injected into the brachial vein, there was a momentary flush, and then an almost instantaneous rise in blood pressure from 140/80 to 200/140. This elevation in blood pressure was associated with a reproduction of all the symptoms and signs of the spontaneous attacks. The test was definitely interpreted as positive. When 0.5 mg. epinephrin were injected subcutaneously, a 20 per cent rise in the systolic pressure occurred, but there were no subjective symptoms.

It was definitely concluded from the above findings that an excess of endocrinologically active chromaffin tissue was present. In the description of the previous operation, it was frankly stated that some of the capsule had been left behind at the previous operation. It therefore seemed most probable that a recurrent tumor was present on the left side, which previously had been operated on.

May 10, 1946, operation was carried out under spinal anesthesia and pentothal. The incision was commenced over the tenth rib at the border of the erector spinae muscles, carried downward and outward over the eleventh rib, about 1 inch above the scar of the previous operation. The eleventh and twelfth ribs were freed from the scar tissue and periosteum and resected close to their articulation. The incision was then carried through the muscles and scar tissue below the pleura, which was clearly visible, carried downward through the lumbodorsal fascia and upward, incising the costovertebral ligament and downward, avoiding the peritoneum. Gerota's capsule was opened and the kidney, which was surrounded by considerable scar tissue, was retracted downward. Above the upper pole of the kidney a soft, vascular tumor measuring about 7 by 4 cm. was found. The adrenal was flattened and stretched out across the tumor, and seemed intimately associated with its capsule. On delivering the tumor there was a rise of blood pressure to 240; the pulse became weak and rapid. A vascular pedicle on the mesial surface of the tumor was clamped, transfixed and ligated with black silk. It was possible to separate a portion of the adrenal from the capsule of the tumor. This was clamped and tied, and about two-thirds of the adrenal removed with the tumor. The stump of the adrenal was transfixed with black silk. On exploration a small nick in the pleura was found, and was closed with fine black silk. The wound was closed in layers in the usual way, without drainage.

The patient left the table in poor condition, obviously in severe shock. During the manipulation of the tumor the blood pressure rose to 240. At the end of the operation it had fallen to 140. The pulse was rapid and weak, and a considerable amount of blood had been lost.

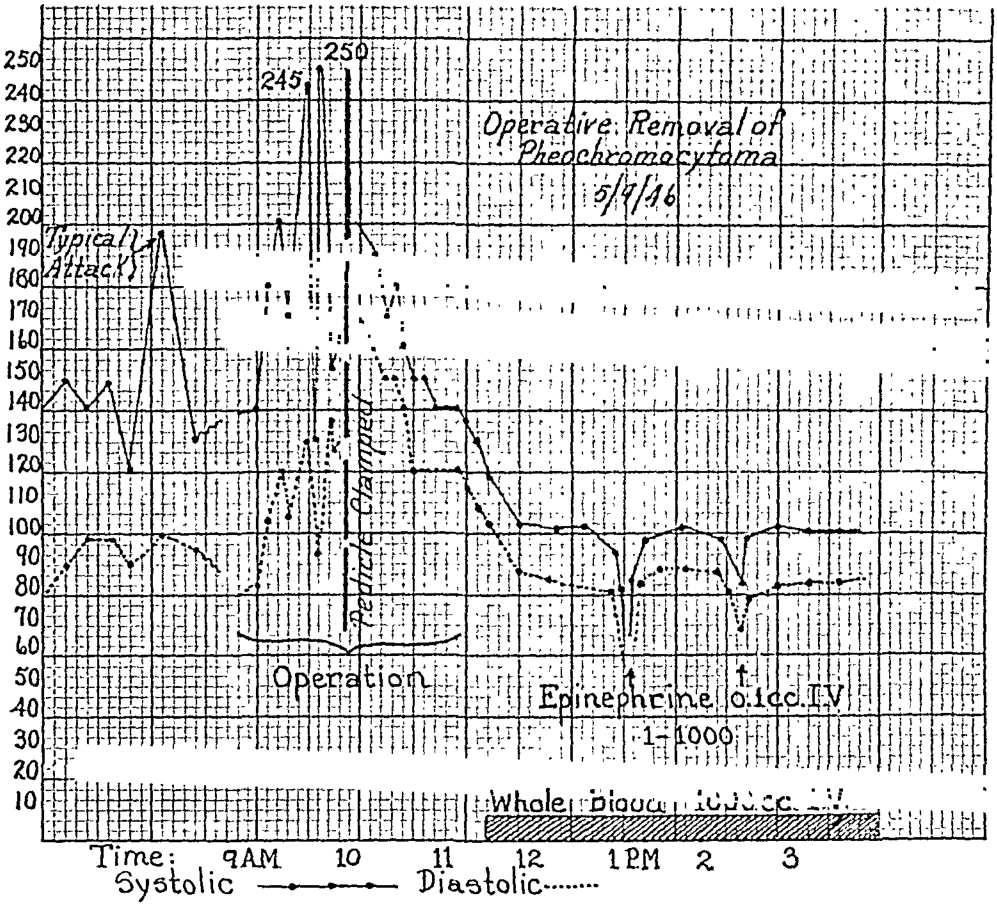

FIG. 1. Case 1. Chart, showing typical hypertensive attack before operation (probably psychic), operation, and immediate postoperative course.

Following operation the blood pressure continued to fall until it reached 80 systolic. Epinephrin, 0.1 cc, was injected intravenously, and a similar dose given 1 hour later. After this the blood pressure remained stable at 100/80 (fig. 1). A litre of whole blood was also administered after operation.

The gross specimen consisted of a bisected piece of tissue 5 by 4 cm., roughly oval in form and covered by capsule, along one side of which ran a thin ridge of yellowish tissue, which, on section, appeared to be a piece of adrenal showing cortical and medullary substance (fig. 2). A large oval tumor was situated at one end of the adrenal and seemed to be continuous with the cortex.

Microscopic section consisted of a piece of tissue at one end of which there was adrenal tissue composed of cortex and medulla, normal in appearance (fig. 3,*A*). The cortical cells themselves contained a great deal of lipoid. Attached to this was a piece of tissue which was composed of large cells with vesicular nuclei, arranged in an acinar pattern. Their nuclei were generally of the same size and shape. The cells contained a great deal of brownish pigment. There was very little mitosis or pyknosis present. The tumor was encapsulated by a thickened fibrous capsule which showed many infiltrations of cells resembling lymphocytes (fig. 3, *B*). Diagnosis: Pheochromocytoma.

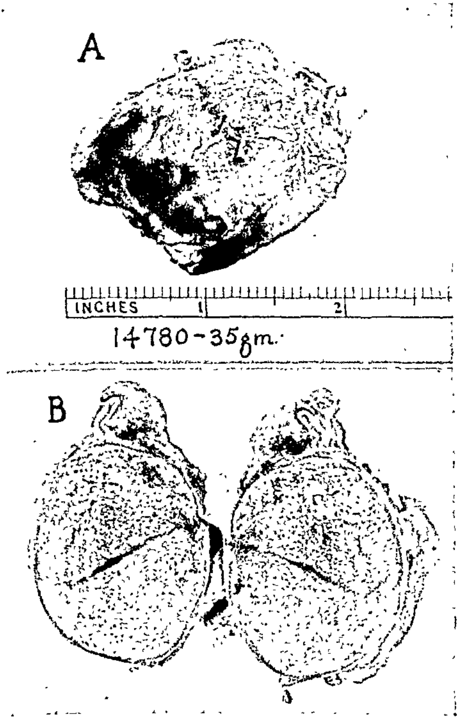

Fig. 2. Case 1. *A*, Tumor removed at first operation. *B*, Tumor bisected. Above and attached to lower pole can be seen cross section of portion of adrenal gland, which is grossly normal in appearance.

On the day after operation signs of left pneumothorax and mediastinal emphysema were apparent. Cyanosis and respiratory difficulty which accompanied these complications were controlled by administration of oxygen. The respiratory problems disappeared after the third day. At this time phlebitis of the right anterior tibial vein became evident at the site of the continuous intravenous injection.

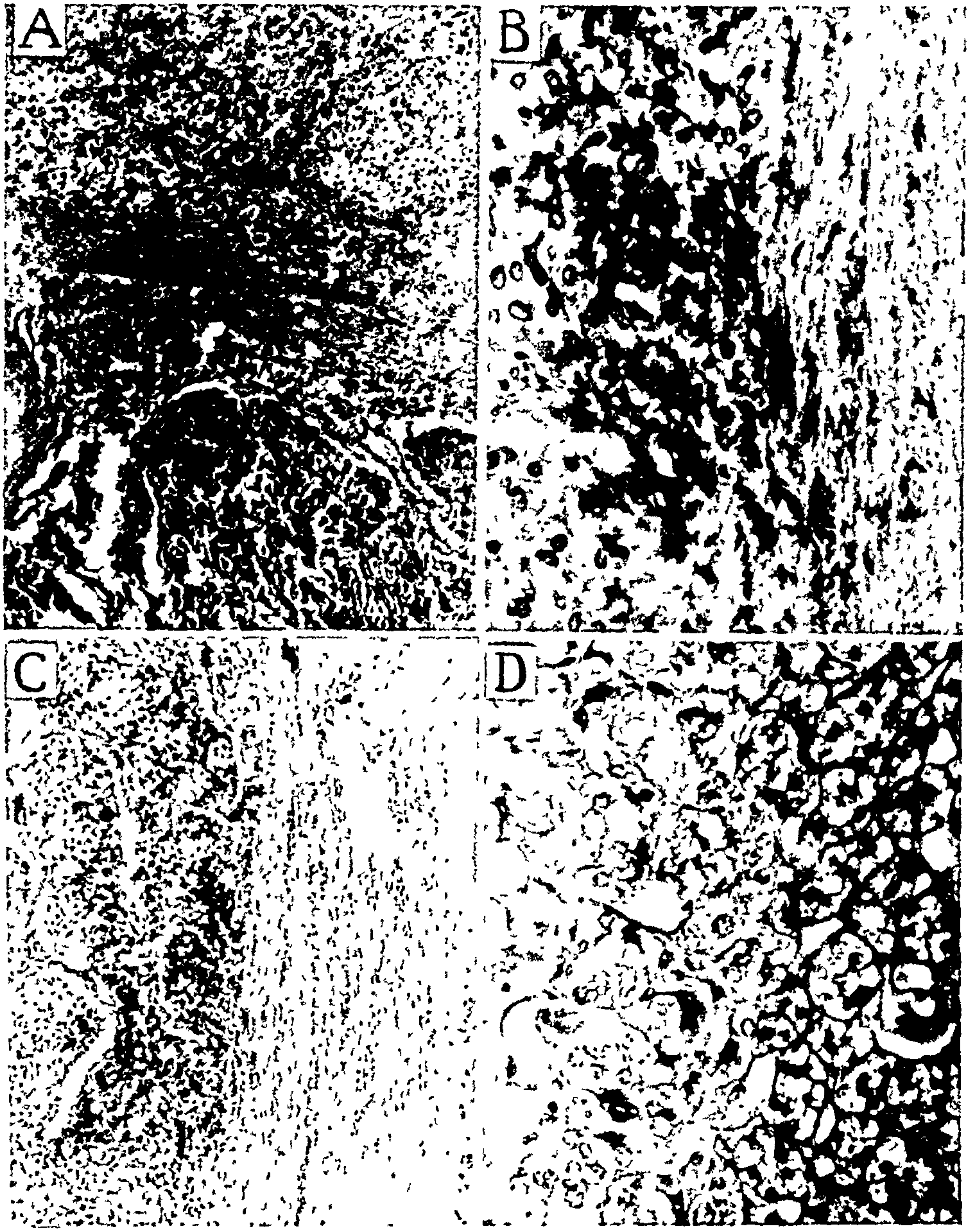

Fig. 3. Case 1 First operation. *A*, Low power photomicrograph, showing typical pheochromocytoma with fibrous capsule, which shows no invasion of tumor tissue. Above capsule can be seen normal adrenal cortical tissue. *B*, First operation. High power photomicrograph, showing typical pheochromocytoma with well defined fibrous capsule. There is no invasion of tumor tissue in capsule. *C*, Second operation. Lower power photomicrograph, showing typical pheochromocytoma with well defined fibrous capsule. There is no invasion of tumor cells in capsule. *D*, Second operation. High power photomicrograph, showing high lipid content of tumor cells with vacuolation and numerous fat droplets

On the tenth postoperative day the patient commented that she felt "woozy" when she lay on her left side. Since this position had evoked attacks before operation, blood pressure measurements were recorded with the patient in the left lateral decubitus. Upon assumption of this position, the blood pressure fell from 130/90 to 90/60, but 90 seconds later the patient exclaimed: "Here it comes!" The blood pressure rose precipitously to 240/170; and the patient complained of nausea and headache, weeping pitifully because she was having another attack after a second supposedly successful operation. As the blood pressure reached its peak 2 minutes after the attack began, there developed flush and profuse sweat and the pulse rate rose to 120, remaining elevated for several hours after the pressure had returned to normal.

Spontaneous attacks of this sort continued to occur when the patient lay on her left side, and sometimes when she assumed the upright position. Intravenous histamine test was repeated (this time using only 0.0125 mg. histamine base), and a typical attack resulted, the blood pressure rising to 210/130. Immediately prior to this test the blood sugar was 118 mg. per cent and the serum phosphorus 4 mg. per cent. Because of the continuing attacks and the positive histamine test, the conclusion was reached that there existed another pheochromocytoma.

The patient was discharged June 1, 1946 and returned on September 23. Meanwhile the attacks had occcurred less frequently but more severely than before.

The physical examination showed the same findings as the first admission. A spontaneous attack was observed 2 days after admission, the blood pressure rising to 220/135. From the clinical picture with recurrent attacks of paroxysmal hypertension and a definitely positive histamine test, it was decided that endocrinologically active chromaffin tissue was still present. As the tumor had been completely removed from the left side without injury to its capsule, it seemed scarcely conceivable that a recurrence could have taken place in this time, especially also in view of the fact that the histamine test was positve 10 days after operation. It was therefore decided that the tumor must lie in the right adrenal area.

A plain x-ray film showed the outline of the right kidney clearly. It was normal in size and position. The contour was smooth. No suspicious shadows were seen in the kidney or ureter. There was nothing to suggest a soft tissue shadow above the kidney. The outline of the left kidney was fairly well seen. It was normal in size and position, and the contour smooth. No suspicious shadows were noted in the kidney or ureter, and there was no evidence of soft tissue shadow above the kidney. The twelfth and eleventh ribs had been resected. A mild scoliosis was present, but the bones were normal.

An intravenous urogram showed excellent excretion of dye from both kidneys (fig. 4). The pelvis of the right kidney was well filled; no dilatation, distortion, filling defect or obstruction at the ureteropelvic junction; calyces cup-shaped and normal. The pelvis of the left kidney was well filled; no dilatation, distortion, filling defect or obstruction in kidney or at ureteropelvic junction.

On September 28, 1946, under ether anesthesia with pentothal induction, an incision was made at the level of the tenth rib, and carried down below the anterior superior spine. The periosteum over both the twelfth and eleventh rib was mobilized, and the ribs resected close to their articulations. Gerota's fascia was then opened, and a normal kidney found. Above the kidney, in the region of the adrenal, a soft mass measuring about 8 by 6 cm. was exposed, which was freely movable. A small tear which occurred in the pleura was closed with silk. The tumor was then delivered into the wound. During this manipulation the pressure rose to 260/120. The adrenal gland was found compressed and thinned out, and intimately associated with the capsule. However, it was possible to separate about one-third of the gland from the capsule, and this was clamped and transfixed, leaving intact the blood supply. The tumor was then delivered, but the capsule was ruptured, and some tissue was extruded. This was immediately swabbed out of the wound. Some vessels coming into the upper medial aspect were clamped and tied, and another blood supply posteriorly was similarly controlled. The tumor then, with its blood supply controlled, and about two-thirds of the adrenal gland attached to its capsule, was removed. The wound was then carefully sponged out to remove any tumor tissue which had extruded from the tear in the capsule, then washed out with ether. The wound was closed in layers with silk.

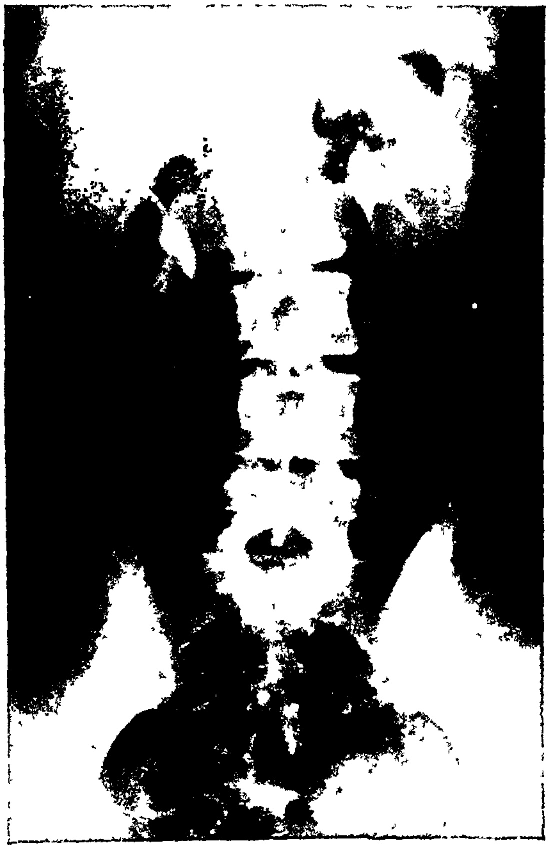

FIG. 4. Case 1. Intravenous urogram taken previous to second operation. Pelvis and calyces of each kidney are well filled, clearly defined, and there is no distortion. Contour of right kidney clearly seen, and no suggestion of soft tissue shadow can be seen above kidney. On left side, twelfth and eleventh ribs have been resected, and upper pole of kidney is not clearly outlined, probably because of postoperative reaction.

The patient left the table in good condition. During manipulation of the tumor the pressure rose to 240/120, but at the end of operation was stabilized at 140 (fig. 5). A transfusion was given during the operation. During the subsequent 4 hours after operation the blood pressure fell to 85/50. Epinephrine chloride, 6 mg., was administered during the first 5 hours and maintained the blood pressure at a normal level.

Pathological examination: The specimen consisted of an irregular mass of tissue measuring about 8 by 10 cm. which was encapsulated, and a piece of adrenal tissue was apparently associated with the capsule. On section the compressed adrenal tissue looked normal. Section of the tumor itself showed a characteristic brownish apperance. (The tumor was sent to the laboratory for biological assay, so no illustration is available.)

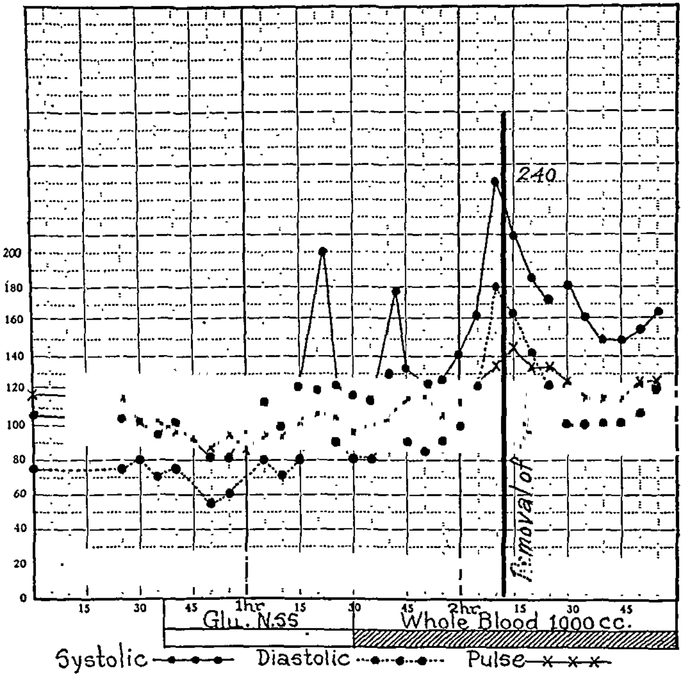

FIG. 5. Case 1. Second operation. Chart of immediate preoperative, operative, and postoperative course, showing typical hypertensive crisis occurring just before onset of operation (probably psychic).

On microscopic section a small piece of normal appearing adrenal was present, the medulla of which was continuous with the tumor growth which had a rather wild appearance with undifferentiated cells. Many large cells were present.

anterior superior spine. The periosteum over both the twelfth and eleventh rib was mobilized, and the ribs resected close to their articulations. Gerota's fascia was then opened, and a normal kidney found. Above the kidney, in the region of the adrenal, a soft mass measuring about 8 by 6 cm. was exposed, which was freely movable. A small tear which occurred in the pleura was closed with silk. The tumor was then delivered into the wound. During this manipulation the pressure rose to 260/120. The adrenal gland was found compressed and thinned out, and intimately associated with the capsule. However, it was possible to separate about one-third of the gland from the capsule, and this was clamped and transfixed, leaving intact the blood supply. The tumor was then delivered, but the capsule was ruptured, and some tissue was extruded. This was immediately swabbed out of the wound. Some vessels coming into the upper medial aspect were clamped and tied, and another blood supply posteriorly was similarly controlled. The tumor then, with its blood supply controlled, and about two-thirds of the adrenal gland attached to its capsule, was removed. The wound was then carefully sponged out to remove any tumor tissue which had extruded from the tear in the capsule, then washed out with ether. The wound was closed in layers with silk.

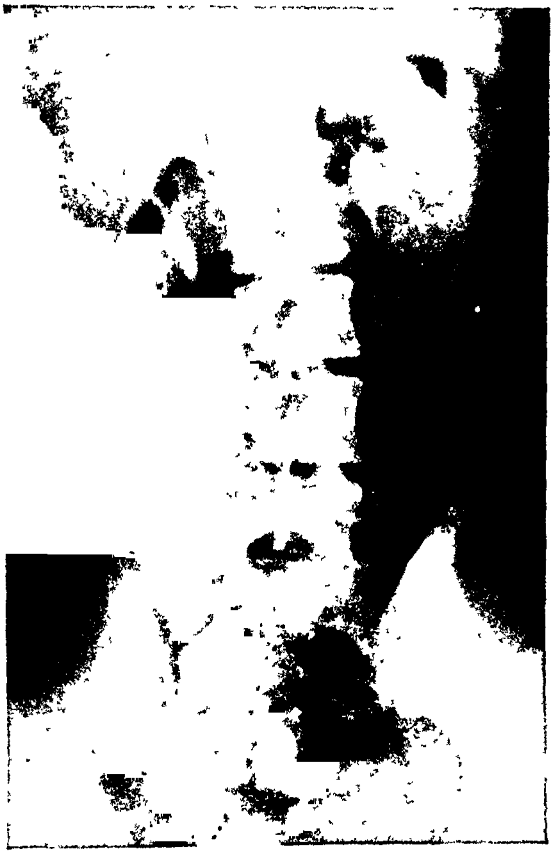

Fig. 4. Case 1. Intravenous urogram taken previous to second operation. Pelvis and calyces of each kidney are well filled, clearly defined, and there is no distortion. Contour of right kidney clearly seen, and no suggestion of soft tissue shadow can be seen above kidney. On left side, twelfth and eleventh ribs have been resected, and upper pole of kidney is not clearly outlined, probably because of postoperative reaction.

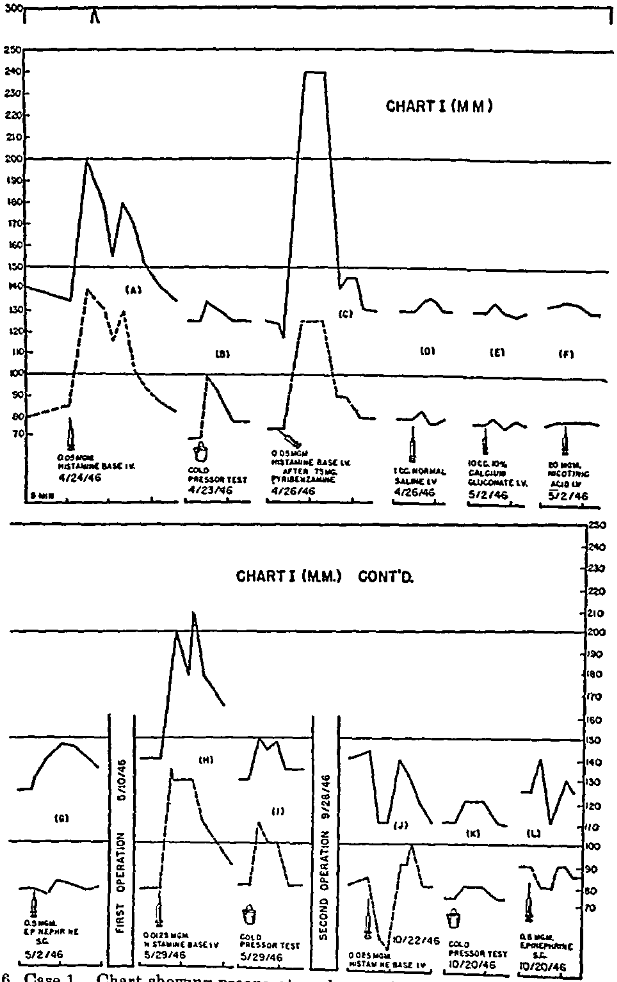

Fig. 6 Case 1 Chart showing preoperative diagnostic measures. Following removal of first tumor, histamine test definitely positive, indicating that active tumor tissue is still present Following second operation, histamine test negative, indicating that all active tumor tissue has been removed.

the kidney were removed. The diagnostic measures and operation at that hospital admission have been reported in detail by Beer, King and Prinzmetal.

The patient was free of attacks for approximately 9 months after the operation. She had suffered with them ever since with the exception of complete freedom during her first pregnancy 7 years before the present admission. During her second pregnancy 4 years before the present admission, however, the attacks were so severe that at the eighth month labor was induced; and a healthy child was delivered manually. The patient was told at that time that her blood pressure was "over 200, and there was albumin in the urine."

During the year prior to her admission to this hospital the attacks were more frequent and severe. She was also troubled by almost continuous sweating and "wave-like feelings of hot and cold." Her symptoms assumed two distinct patterns, sometimes one merging into the other, but more often occurring separately. In type 1 there were "headache, blanching of the skin, pounding of the heart, goose pimples and a sensation of hair standing on end." Such attacks were quite regularly induced by exertion and lasted only a few minutes. In type 2 she experienced a feeling of weight in the chest, pain in the episternal notch and down the left arm. Attacks of this sort might last throughout an entire day. Menses were quite regular and normal, and there had been no recent change in weight.

Physical examination revealed a hyperkinetic woman who appeared in good health. Nutrition was normal, and there was no abnormal pigmentation. Examination of the optic fundi revealed narrowing of the fundal arteries and slight nicking of the veins at the crossings. There was no papilledema, and no exudates or hemorrhages were seen. The thyroid tissue beneath the scar was normal to palpation, and there were neither eye signs of Graves' disease nor tremor. There was no lymph node enlargement. The lungs were clear. The heart was overactive but not enlarged; sounds were vigorous, and there was present a rough systolic murmur, loudest at the apex, interpreted as of organic, probably rheumatic, origin. The right kidney was enlarged, readily palpable and not tender. The liver was at the costal margin; the spleen was not felt. Reflexes and peripheral pulses were normal. When the patient was examined while symptom free (except for the almost constant sweating), the blood pressure was highly variable, ranging from 120/80 to 250/140. The cardiac rhythm showed frequent curious changes of which the patient was quite unaware, seemingly unrelated to the blood pressure fluctuations. The rate might be found as low as 50 per minute, with abrupt changes to 140 to 150 per minute, and might be either regular or irregular.

During attacks the following observations were made: Skin pallid and drenched, dyspnea with respiratory rate up to 50 per minute, extreme weakness and mental confusion, much like a patient coming out of an anesthetic. The blood pressure was as high as 280/160, but it should be noted that in such spontaneous attacks the blood pressure was always falling by the time the observer reached the patient, and it may well have reached higher levels.

The patient was discharged from the hospital after only 4 days, because her child became ill. She returned on September 30, 1946 with symptoms unchanged and physical findings identical. On both admissions she ran a slightly elevated evening temperature (100 to 100.4° per rectum) before operation.

The laboratory data and special studies have been completely described by Calkins and Howard, and only positive findings will be recorded here. The phenolsulphonphthalein test showed a definite diminution of 15 per cent in the first 15 minutes and a total of 55 per cent in 2 hours.

On plain x-ray the outline of the right kidney was fairly well seen, slightly larger than normal, slightly lower in position, contour smooth. The outline of the left kidney was not seen.

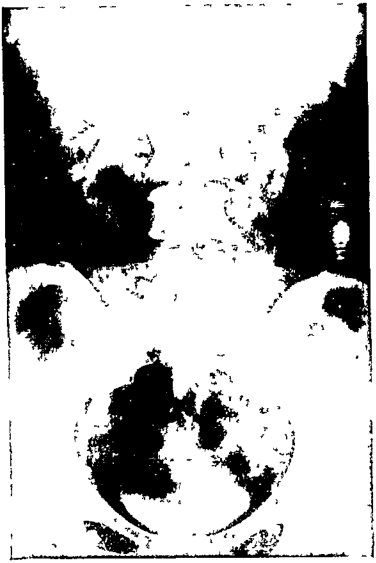

FIG 7. Case 2. Intravenous urogram. Pelvis of right kidney well filled, slightly dilated. Calyces are clearly defined, cup shaped and normal, but upper calyx has been displaced caudally. Contour of kidney is not clearly seen, but above it a soft mass is apparently present. There is no function on left side.

The 5 minute intravenous urogram showed good function on the right side; none on the left. The 15 minute film showed the right kidney well filled, moderately dilated, no distortion, filling defect or obstruction at the ureteropelvic juncture. The calyces were a little larger than normal, but retaining normal cupping. The upper calyx seemed pushed in a downward direction. Above the kidney could be seen what might be interpreted as a large, soft tissue mass (fig. 7).

In the cold pressor test the blood pressure rose from 135/90 to 160/105. When 0.05 mg. histamine base was injected in 10 cc saline, an immediate flush occurred, with fall of blood pressure from 140/100 to 95/80. Within a minute the blood pressure had risen to 300/90. The skin was pale, respirations were 90 and pulse 150 per minute. The patient's symptoms were the same as during a severe spontaneous attack. Bending, lateral flexion and jumping produced no change in symptoms or blood pressure. Strenuous exercise produced a severe attack but not the curious electrocardiographic pattern, as described by Calkins and Howard.

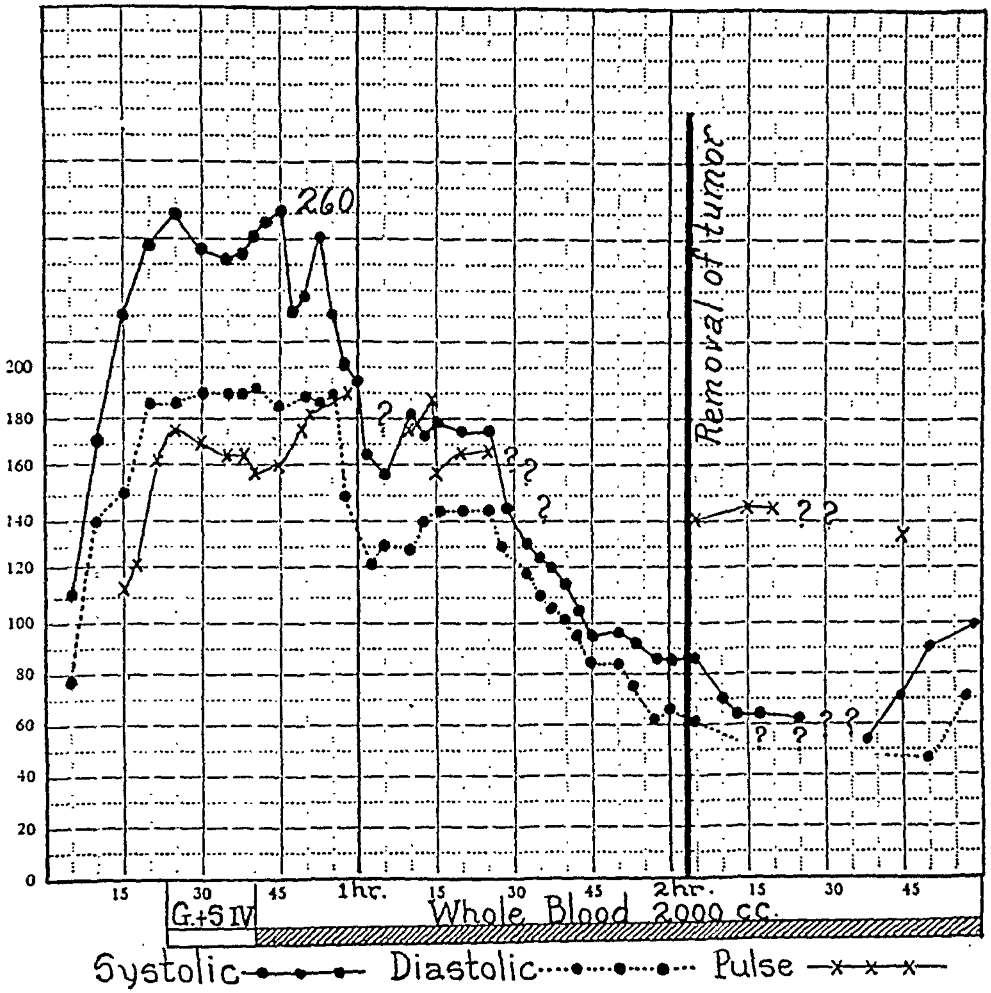

FIG. 8. Case 2. Chart, showing extreme shock when tumor and portion of adrenal gland were removed. Slow recovery from shock by transfusion of whole blood.

From the above findings it seemed evident that an excess of physiologically active chromaffin tissue was still present. As the tumor with the entire left adrenal gland had been removed from the left side, it was decided that the right side should be explored. It must be remembered that the entire adrenal had been removed from the left side so that the operation was undertaken with considerable trepidation, as of course, it was urgently necessary to preserve as much adrenal as possible.

Ether was administered with vinethene induction. The incision was commenced over the tenth rib and continued parallel with the sacrospinalis muscle and then outward above the anterior-superior spine. The twelfth and eleventh ribs were exposed, stripped of their periosteum and resected close to their articulation. The lumbo-dorsal fascia was opened downward and upward, including the costovertebral ligament. When Gerota's fascia was opened a large but otherwise normal appearing kidney was exposed. Above the kidney could be felt a very large tumor about the size of a grapefruit. This was well encapsulated and gradually separated from the surrounding structures. As in case 1, the adrenal was found spread out over the lower and medial portion of the tumor and intimately attached to the capsule. The upper and medial portion of the adrenal, however, apparently about one-third, was uninvolved and could be separated from the capsule of the tumor, and was clamped as close to the capsule as possible, divided, and the stump of the adrenal, with the blood supply intact, was preserved. The capsule in the upper portion of the tumor was ruptured, and some tumor tissue extruded. This was wiped out, and the tumor removed by clamping the remaining vascular attachments. Two small tears which occurred in the pleura were closed immediately with medium silk. When the tumor was removed all bleeding had been satisfactorily controlled. The wound was then washed out with alcohol, followed by ether and salt solution.

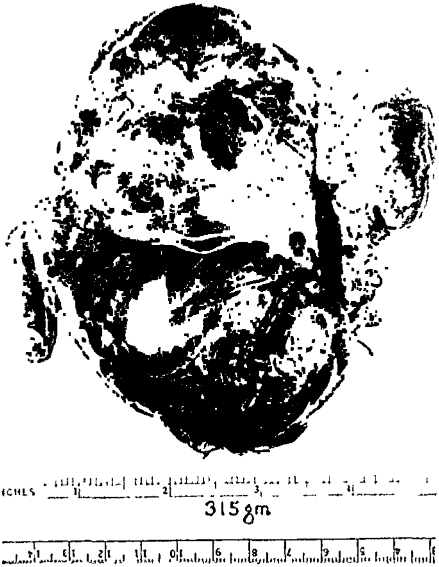

FIG 9 Case 2 Gross specimen. At upper border of tumor on right side can be seen some adrenal tissue, normal in appearance, that was incorporated in capsule of tumor.

A rather large tear was then found in the diaphragm which was closed with interrupted mattress and medium silk. The muscles were closed in layers, and a Penrose drain placed down above the kidney. The patient was severely shocked. The pulse at one time was unobtainable, the blood pressure being at times very low. A transfusion and adrenalin were given. The patient was put in the Trendelenberg position. The pulse steadily improved, and the systolic pressure was 90 when she was taken back to the ward. A considerabl amount of blood had been lost (fig. 8).

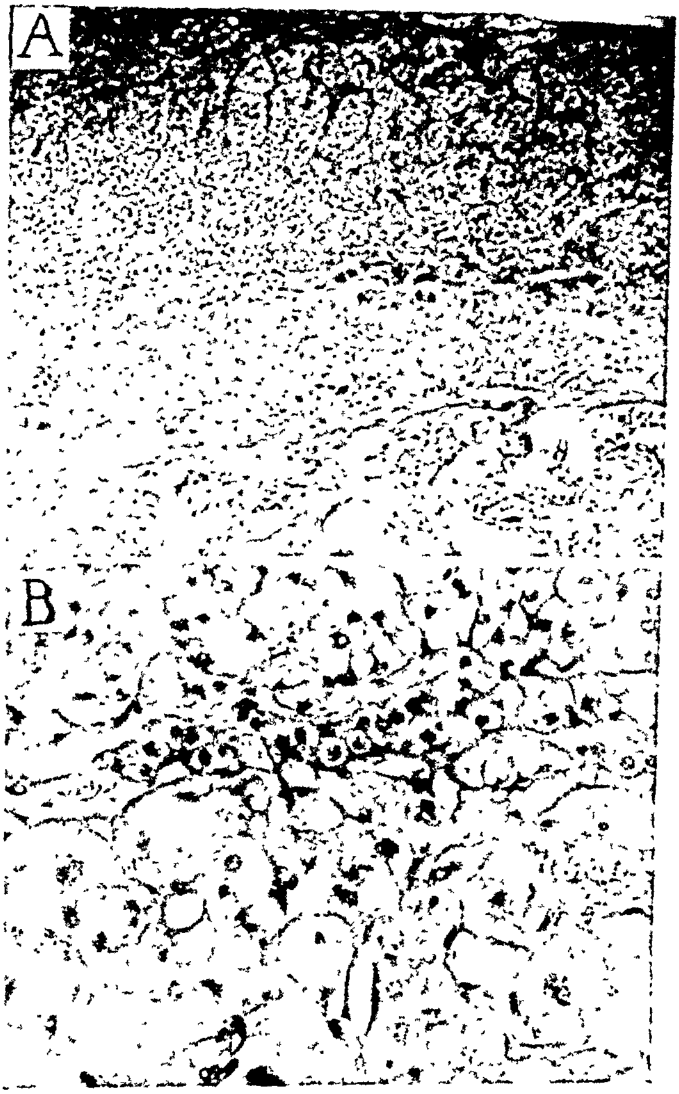

FIG. 10. Case 2. *A*, Low power photomicrograph, showing edge of tumor, and above it normal adrenal cortical tissue. There is little or no capsule between tumor and adrena tissue. *B*, High power photomicrograph of tumor tissue, showing same characteristics a noted in case 1.

The postoperative course was stormy, the fever reaching 105 on the secon night, and at this time a pneumothorax was evident, which was tapped. Tl patient was dyspneic and cyanotic for several days, but after the fourth day h improvement was rapid, and the blood pressure became stabilized. There was some wound infection and phlebitis at the site of the intravenous infusion.

Pathological examination showed the mass (fig. 9) to be a pheochromocytoma surrounded by a thin layer of adrenal cortical tissue (fig. 10). The tumor cells were similar to those in the second tumor removed from M. M., but no tumor cells were found within the blood vessels.

Two weeks after operation there was no clinical or chemical evidence of renal insufficiency. The histamine test was repeated and considered negative (fig. 11).

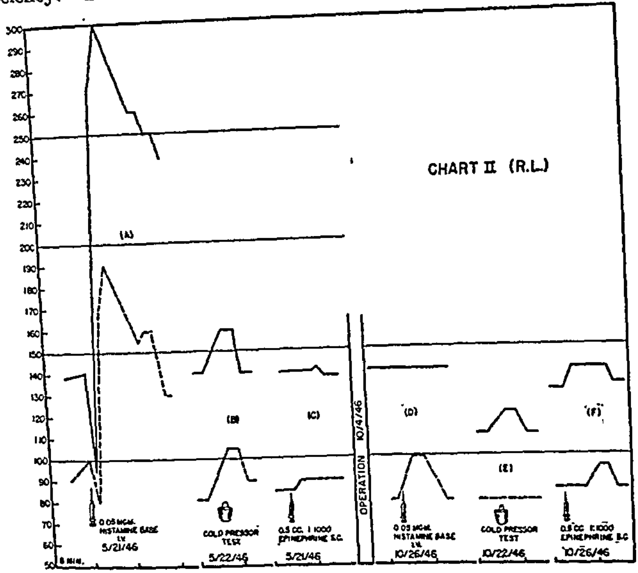

FIG. 11. Case 2. Preoperative and postoperative diagnostic measures. Markedly positive reaction occurs from injection of histamine base before operation. After removal of tumor, same test is negative.

The preoperative diagnostic procedures and the postoperative follow-ups are shown in figure 11, after the chart prepared by Calkins and Howard.

A letter from the patient 4 weeks after operation (February 6, 1947) stated: "Anything resembling previous attacks has completely disappeared. The blood pressure is 120/80. Absolutely no sweating, and I am quite strong. My circulation does not appear to be normal however. My hands blanch from the palms to the fingers, and at times the tip of my nose is usually cold." These symptoms of Reynaud's disease had been present since the age of 18, and had not been materially altered by her first operation.

The patient has recently been through a normal pregnancy, and gave birth to a normal child. Letter (January 8, 1948): "This pregnancy has been most uneventful. My pressure remains at 115/80 or less. Everything has been very satisfactory."

SUMMARY

Two unusual cases of bilateral pheochromocytomata in blood relations are reported in full. In case 1 a pheochromocytoma had been removed 4 years previously at operation elsewhere, but owing to technical difficulties, it was necessary to leave behind a portion of the capsule. A recurrent tumor apparently developed from this portion of the capsule, and was successfully removed by operation. The hypertensive crises, however, still persisted, with a positive histamine test 4 months later. A second pheochromocytoma was exposed at operation on the opposite side and successfully removed.

The patient's maternal aunt had been operated on elsewhere 9 years previously, and a pheochromocytoma, the entire adrenal and the left kidney removed. She was relieved of symptoms for 9 months, but the hypertensive crises recurred. A diagnosis of pheochromocytoma on the opposite side was made, and at operation a large tumor was exposed and successfully removed.

The diagnostic value of the histamine test has been emphasized.

The technical difficulties at operation are discussed, and the suggestion advanced that the exposure of both adrenal areas might be more satisfactorily carried out through an upper transverse abdominal incision. The advantages of such an approach are obvious, providing sufficient exposure can be obtained to remove a tumor if one should be encountered.

This report is intended in no sense to be a complete follow-up, but case 1 has now been well for 17 months, has had no further hypertensive crises, and the histamine test is negative, so that as of to date it might be safely concluded that no further excess of physiologically active chromaffin tissue is present.

Case 2 reports that she has been well in every respect, and has had no return of hypertensive crises for a period of 16 months. The histamine test has not been repeated in this case, but the patient has recently been through a normal pregnancy with delivery of a normal child, and reports that her blood pressure has never been above 115 systolic and 80 diastolic.

I wish to express my appreciation to Drs. Evan Calkins and John Eager Howard of the Department of Medicine for their courtesy in making available the complete clinical records of these patients.

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SOMATIC PAIN DUE TO FIBROLIPOMATOUS NODULES, SIMULATING URETERO-RENAL DISEASE: A PRELIMINARY REPORT[1]

LOUIS M. ORR AND (by invitation) FRED MATHERS, AND THOMAS C. BUTT

The diagnosis of many disease processes is based upon a careful analysis of the associated pain. This is particularly true in urological diseases. We have for so long been impressed with the reference of visceral pain to the external dermatomes of the body, or along the course of cutaneous nerves, that we seldom think of somatic pain as being of etiological significance until all studies of the suspected viscera fail to reveal a cause for the pain. This is no doubt due to our being conditioned by long years of thinking of visceral referred pain to the neglect of an understanding of somatic pain. Most investigational work in the past has been in relation to pain referred from viscera and the neurological pathways have been carefully charted.

It is the purpose of this discussion to present a not uncommon mechanism for the production of symptoms simulating disease of the urinary tract which is not generally known and frequently overlooked as illustrated in the cases to be presented.

Sir Thomas Lewis, in discussing pain of visceral disease, states that Mackenzie's concept of referred pain was best explained by the fact that viscera are tissues which have no true positional sense or detailed respresentation in the cortex. His hypothesis can be briefly stated in this manner: The impulses from the visceral structure on reaching the sensorium are interpreted as pain and the pain is referred to the cutaneous segment or dermatome in default of sharper localization. In this paper we are dealing only with the D-12, L-1 and L-2 dermatomes. Lewis further states that there is no reason and no gain in distinguishing in any fundamental way between nerves conveying pain from deep somatic structures or from sensitive visceral structure. Physiologically and antomically, pain fibers supplying the two types of tissues are alike and the fact that those from somatic structures at first use the channel of the spinal nerve and that those from the visceral structures at first use the channel of the anatomical sympathetic system before entering the posterior roots is really immaterial. The innervation of the kidney and ureter has been described by Kuntz and will not be reviewed.

The British investigators, Copeman and Ackerman, dissected the backs of 14 cadavers during World War II in an effort to determine the legitimacy of complaint in soldiers who presented characteristic symptoms of myositis or fibrositis of the lower back. A constant and definite finding were deposits of fibrofatty tissue which occurred beneath the superficial fascia in well defined areas, even in grossly wasted bodies in which most of the body fat elsewhere had disappeared. They termed this consistent localization of fat "the basic fat pattern." It was noticed that the fascia was not of uniform thickness and in certain places there were actual deficiencies present through which small lobules of fat were seen to herniate. It was likewise found that the cutaneous branches of the lumbar nerves, accompanied by blood vessels, pierce this fascia through definite foramina after leaving the muscle. Not infrequently were lobules of fat seen partially herniated into these foramina.

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., June 30, 1947.

In an examination of 65 soldiers presenting symptoms of lumbar fibrositis, Copeman and Ackerman found well defined, painful nodules along the lower borders of the erector spinae muscles and the crests of the ilia. These points of tenderness they designated as "trigger points." The location of these trigger points followed a constant grouping which they designated as a "pain pattern." This pain pattern of the back and gluteal region corresponded in anatomical relationship to the "basic fat pattern" of the same region. They found the nodules to contain fatty and fibrous tissue to which they gave the term "fibrositic." They further stated that because of the exigencies of warfare no special stains for nerve fibers were made.

Mathers and Butt have since located fibrolipomatous nodules at numerous points in the cervical and dorsal regions along the borders of and over the surface of the erector spinae muscles. From their studies, to be published at a later date, they question the herniation of fat lobules through nerve foramina and believe that painful fat nodules represent a local pathologic process in the normal layer of body fat which lies over the muscles of the back when the local disturbance is such as to cause pressure upon one or more of the cutaneous nerves.

Whereas Copeman and Ackerman were concerned with the pathology and etiology of true myositis and fibrositis of the back, our further studies have revealed these nodules as being a source of pain and an etiological factor in the production of symptoms simulating true ureteral and renal disease. Because of the histology of these nodules (fig. 1) we have elected the term "fibrolipomatous" rather than "fibrositic" as being more descriptive of the nodule.

These nodules (fig. 2) are palpable to the examining finger and pressure will produce the pain complained of and oftentimes stimulate distant referred pain such as that arising from disease within a viscus. Local injection of novocaine directly into the nodule will eliminate the pain to the complete satisfaction of the patient. Surgical removal of the nodule has resulted in permanent relief of pain, both local and referred.

In that we are here concerned only with a discussion of those sources of somatic pain simulating ureterorenal disease, we must be confined necessarily to irritating foci affecting the twelfth dorsal and/or the first and second lumbar dermatomes. It must be kept in mind that these nodules represent only one type of irritant which may produce somatic pain which simulates ureterorenal disease. The report of the case by Wills and Atsatt in which ureteral spasm was relieved by correction of the irritating focus about the spinal articulation of the first lumbar vertebra illustrates another cause of somatic pain.

Ussher, in 1933, described the original concept of viscerospinal syndrome (fig. 3). His concept was that points of irritation (cutaneous, muscular, articular) are primarily stimulating postganglionic fibers supplying a viscus resulting in spasm of smooth muscle which in turn reflects itself as disturbance in normal physiology of the involved organ. This is a reversal of the old concept that irritative processes in viscera produce reflex spasm of striated muscles which receive innervation from the same level of the spinal cord. In 1940, he presented a large series of cases in which smooth muscle spasm was a basic pathologic disturbance which was fundamentally due to irritations of posterior branches of cutaneous nerves because of articular disturbances. This concept has not received general recognition.

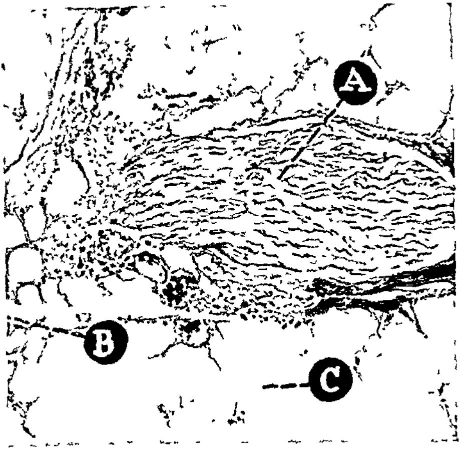


FIG 1. Histological structure of a fibrolipomatous nodule: *a*, Nerve fiber; *b*, connective tissue; *c*, fatty tissue.

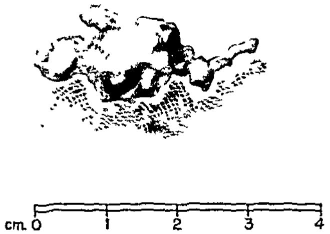
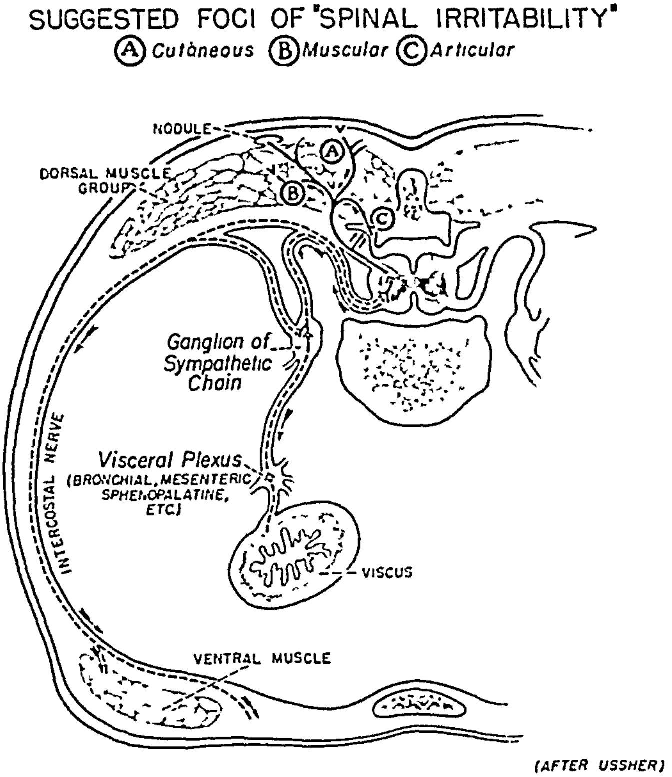


FIG. 2 Diagramatic sketch of a fibrolipomatous nodule

This brings up the question: Can actual disturbance in kidney physiology such as the secretion of urine be produced by these nodules, and can the function of the ureter and bladder as regards motility or smooth muscle spasm be disturbed?

Two of our cases presented frequency of urination which were relieved by removing the nodules, and one was also relieved of bouts of ureteral spasm which were of such intensity to warrant cystoscopic examination on three occasions with fruitless effort. Future work is required to prove or disprove the hypothesis which is, as yet, based purely on clinical observation. The difficulties of such proof are obvious because instrumentation of the urinary tract is in itself productive of physiological changes. It is planned to investigate this in the future.

We know that spasm of the loin muscles can be produced by stimulating the healthy ureter or renal pelvis, as shown by Ockerblad and Carlson and substantiated by McLellan and Goodell, and that the spasm persists long after the stimulus is withdrawn. It is not too fanciful to expect visceral changes when these muscles are thrown into spasm by somatic impulses.



SUGGESTED FOCI OF "SPINAL IRRITABILITY"

Ⓐ *Cutaneous* Ⓑ *Muscular* Ⓒ *Articular*

NODULE
V
A
DORSAL MUSCLE GROUP
B
C
Ganglion of Sympathetic Chain
INTERCOSTAL NERVE
Visceral Plexus (BRONCHIAL, MESENTERIC, SPHENOPALATINE, ETC)
VISCUS
VENTRAL MUSCLE

(AFTER USSHER)

FIG. 3. Showing chief components of viscerospinal syndrome. A fibrolipomatous nodule is depicted as a focus of irritability in addition to *A*, *B*, and *C*. From these foci afferent impulses are carried to the cord by dorsal nerve roots. Synaptic connections are shown relaying impulses through ventral roots to viscus by way of viscero-efferent sympathetic network. (Ussher)

The cases to be presented represent our original observations of causes of renal and ureteral pain originating in somatic structures in the form of fibrolipomatous nodules in patients who were studied repeatedly with negative pathological findings by the usual procedures employed in the diagnosis of urinary tract pathology.

CASE REPORTS

Case 1. J. M. S., a man aged 25, stated that in January 1945, while in the armed forces, he had a sudden, moderately severe pain in the right costovertebral region radiating to the genitalia. He was told that red blood cells were found in the urine. Studies in a military hospital with cystoscopic examination and retrograde pyelograms did not disclose any cause for the symptoms. Similar episodes later occurred and urological investigations were performed on two other occasions with normal findings. He continued to have an almost constant pain in the right costovertebral angle. Since discharge from the service, this pain has become exaggerated whenever he attempted to drive a tractor or truck and has been relieved only by complete rest.

Physical examination revealed a slight pitting edema of the left ankle as a residuum of phlebitis which had occurred in 1941 and a palpable, tender nodule at the lateral edge of the right erector spinae muscles at the level of the twelfth dorsal vertebra. Pressure on this nodule produced pain with radiation to the anterior abdomen and right groin. He stated that this pain was identical with the previous pain for which he had been cystoscoped three times since 1945. Injection of novocaine into the nodule produced complete temporary relief of symptoms. Permanent relief of pain was secured by surgical removal. Frequency of urination, which had been of minor importance, was relieved.

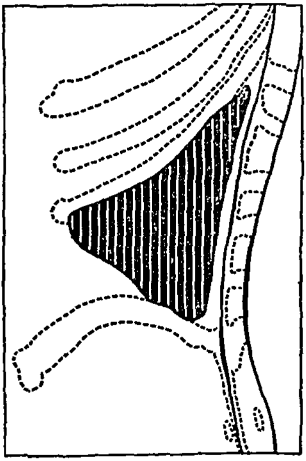


FIG. 4. Pain distribution in case 2 (shaded area)

Case 2. Mrs. L. R., aged 38, had had pain in the left kidney region for the past 7 years. The pain was described as dull and constant, originating in the region of the left kidney and extending over the area as shown in figure 4.

During the initial attack of pain 7 years ago, the presumptive diagnosis of renal calculus was made. Cystoscopic examination at that time was reported negative, and she was told the stone had probably passed. Subsequent to this attack, she continued to have the sensation simulating renal colic. Cystoscopy on 4 different occasions, with complete urographic studies, were reported negative. Since the date of the first attack of pain, the patient had undergone an appendectomy and right oophorectomy without relief of symptoms.

The patient was first seen by one of us (F. M.) in February 1947. A painful, palpable nodule was found at the level of the second lumbar vertebra, 3½ cm. to the left of the midline. One cc of novocaine was injected and the patient experienced completed relief. As she expressed it: "My kidney stone is gone."

Three weeks after the initial injection, the pain returned and she was advised to have the nodule excised. On March 20, 1947, the mass was excised. The following day the patient was free of pain. Examination a short time ago revealed that she still has complete relief of pain.

Case 3. Mrs. D. L., aged 36, had pain in the right kidney region. The patient stated that 14 years ago, while riding horseback, she had a sudden twist as the horse stumbled which was followed by pain similar to that complained of at present. This pain was described as a dull, aching pain which extends from the right costovertebral angle to the right lower quadrant of the abdomen. There was no complaint of dysuria, frequency, or hematuria. The pain was more severe when sitting, and was not relieved by heat, although gentle massage at times gave partial relief. Mild sedation was frequently required. She had been cystoscoped repeatedly, and in 1941 underwent a right nephropexy. Other than ptosis of the right kidney which was successfully repaired, the urological examinations were repeatedly negative. During the past 7 years, the patient had been carefully followed by urologists, orthopedists, gynecologists, and general practitioners. Three pregnancies have been successfully completed, 17 years, 4 years, and 8 months ago. During the past 6 months, the pain in the right kidney region had continued unabated. Careful examination had revealed no cause for this pain until a nodule was found in the region of L-2, 4 cm. to the right of the midline. Pressure over this site reproduced the pain which the patient has complained of and injection of novocaine into the site of the palpable tumor mass produced complete relief for 5 years.

The patient was recently admitted to the hospital and a fibrolipomatous tumor was removed with repair of a small fascial hernia. Up to the present, the patient has had complete relief of pain which had been endured for 14 years.

Case 4. C. G., aged 27, was referred by an urologist for investigation of a possible painful nodule in the left lumbar region. He complained of pain in the left testicle. On March 29, 1947, the patient stated that he had a pain in his left testicle, associated with frequency of urination, which radiated from the testicle to the left lumbar region. The pain was dull and aching in type and would seem to go through the left side of the abdomen from the testicle to the region of the left kidney (fig. 5). The patient stated that at times the pain had seemed colicky in nature, although usually it was a constant "toothache" type of pain. Prior to this attack, excellent health had been enjoyed and no pain similar to the present had been experienced. In 1942, the right testicle was removed because of cryptorchidism.

Examination was negative other than absence of the right testicle and a tender area in the left side of the back 5 cm. from the midline between L-1 and 2.

Pressure over this point produced pain which was referred to the left testicle. Complete urological examination was negative for pathological changes. At no time did the patient have any tenderness on palpation of the testicle or spermatic cord.

Preliminary injection of novocaine relieved the pain completely. On May 30, 1947, the nodule was excised. When last seen the patient stated that the pain in the left testicle and back had been completely relieved.

Case 5. Mrs. B. P., aged 34, had had pain in right side of the back for 12 years. The patient stated that the pain extended from the right costovertebral angle and to the right lower quadrant. Five years ago, an appendectomy was performed for the relief of this pain without benefit. Four years later, a laparotomy for adhesions resulted in no benefit. During the interval between these operations urological studies had been negative. In 1947, the pain had become constant and more severe upon fatigue but on admission the pain had become so severe that she was unable to carry on her household duties. Following the second operation, an orthopedic surgeon made the diagnosis of arthritis and neuritis and she had received treatment in the form of physiotherapy, sedation, estrogens, etc., without relief. Urological examinations had not revealed a cause for the pain. In 1947, the patient became "desperate" and underwent a thorough examination in a well-recognized clinic. Nothing was found to account for the pain. Upon return home, urological studies were again carried out with normal findings. A gynecologist later stated that she had a "tipped womb."

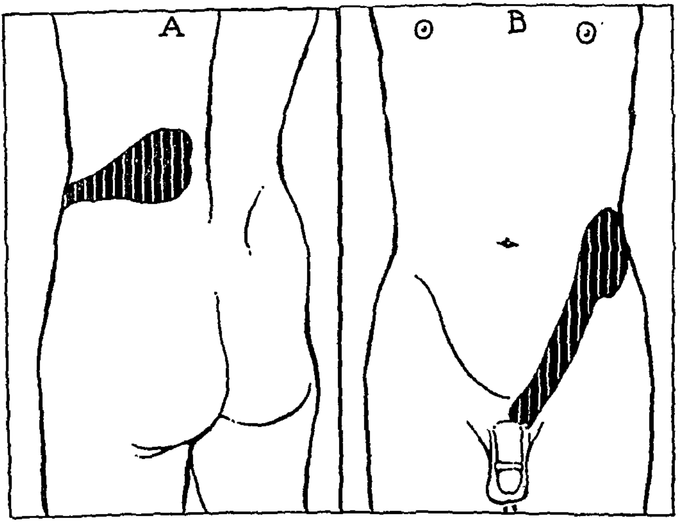


FIG. 5. *A*, Dorsal and *B*, ventral distribution of pain in case 4

Physical examination revealed a very tender localized area in the region of L-2, 3 cm. to the right of the midline; nothing else was found after a careful examination. Urinalysis and complete blood count were normal. It was felt that the pain complex could be accounted for by the localized area of tenderness. Due to excessive fat in the region of the painful area it was impossible to definitely palpate a nodule. However, following the injection of 3 cc of 1 per cent novocaine on 2 occasions at weekly intervals, there was complete relief of pain for 48 hours. Subsequently, an exploration of the back revealed a fibrolipomatous nodule which was excised. This mass was exceptionally large, measuring approximately 3 by 2 by 5 cm. The operation was followed by complete relief of pain up to the present time.

SUMMARY AND CONCLUSIONS

We have for so long been conditioned in our thinking of visceral pain being referred to the external dermatomes of the body that we have become neglectful in our understanding of somatic structures as being the site of pain impulses which can simulate visceral disease. The original concept of the viscerospinal syndrome as presented by Ussher in 1933, now a recognized entity, pictured the reversal of the process in which impulses originated within the viscus and thence being referred to the skeletal structures. The British investigators, Copeman and Ackerman, in dissecting cadavers in search of an anatomical cause for the presence of "fibrositic nodules" or "myalgic spots" in the backs of soldiers complaining of myositis and fibrositis, described the "basic fat pattern" of the back. The fat pattern corresponded to the "pain pattern" formulated after a study of the backs of 65 unselected cases with myositis.

Our additional studies have located nodules in those body dermatomes of the twelfth dorsal and first and second lumbar vertebrae. Clinical investigation of nodules in these locations have revealed them to represent a somatic cause for pain which simulated ureteral and renal disease, after a careful search of the urinary tract had revealed no evidence of disease. Because of the histologic structure of the nodules, we have elected the term "fibrolipomatous" rather than "fibrositic" as given by Copeman and Ackerman. Nerve fibers have also been demonstrated in the nodules which were not previously described. Although it is not within the limits of this paper to discuss possible alterations in renal physiology by somatic irritation, it does not seem too fanciful to expect visceral changes as a result of somatic impulses. Consideration of such possibilities offers a definite challenge to further investigation.

Except in the very obese patient the nodules are usually quite easily palpable and are painful to pressure. Oftentimes pressure will reproduce distant referred pain. Under local anesthesia pinching of the exposed nodule will cause radiation of pain to the ureter, kidney or testicle, depending upon the segmental location of the nodule.

In all patients who present pain which simulates ureterorenal disease, and in whom no evidence of urological pathology to account for the pain can be found, a careful examination of the back may result in finding a somatic cause for the pain in the form of a fibrolipomatous nodule.

Several case records of patients have been presented who complained of renal and ureteral pain without evidence of urological pathology after repeated investigations in whom fibrolipomatous nodules are found at the level of D-12, L-1, and L-2 vertebrae. Removal of the nodules resulted in complete relief of pain up to the time of this report.

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DISCUSSION

Dr. Stanford W. Mulholland (Philadelphia, Pa.): Dr. Orr's paper would seem to give us a little different slant on ourselves. The urologist is often quite "smug" and feels his is a very exact specialty. "If no pathology is demonstrable in the urinary tract, there is none." Dr. Orr has demonstrated to us we must not stop looking and examining even when pyelograms are normal.

The explanation of referred pain suggested by Sir Thomas Lewis is fascinating and logical. Pain impulses come from a viscus through the sympathetic afferent fibers or from somatic areas through the dorsal nerve roots. After reaching the cord they may spread to the gray matter. Here they can disturb pain tracts reaching the cerebrum from the same or close segments of the cord. This means the localization for pain in the cerebrum is not clear cut, otherwise they could be identified more accurately. Apparently a general rather than a *detailed segmental localization is present.* The efferent impulses travel through the same trunks but may be switched either way, to viscus or to skeletal structures. We have come to think of loin pain as renal pain and costovertebral tenderness as meaning kidney disease.

I believe one of the most thought provoking ideas in this paper is, just what pathological changes might occur in the urinary tract as a result of these fibrolipomatous structures? We often see many strictures of the ureter, kinks and redundancy, the cause of which are not evident. No doubt a urological examination is incomplete until we have assured ourselves that lesions such as described by Dr. Orr have not been the cause of demonstrated abnormalities.

In 1921 Lange and Schade in discussing the occurrence of firm, painful nodules in muscles, introduced the term "myogelosis". Since the histological examination of the nodules has been essentially negative, their exact nature appears speculative. They do not disappear under deep general anesthesia; hence it is probable they are not purely local spasms in muscle but the results of organic changes of a colloido-chemical nature. Other observers have found fibroblastic proliferation as would be expected in any local disturbance persisting for a prolonged period of time.

The industrial surgeon is well aware of these possibilities and mechanisms of referred pain. Slobe states: "The primary zone of local infiltration in a injured muscle with its altered local metabolism and relative ischemia, stimulates sensitive nerve fibers giving rise to pain, tenderness and perhaps muscular spasm and by acting as a 'trigger zone' frequently causes pain referred to distant areas."

The physician treating occupational diseases knows the un-natural use of certain groups of muscles, incorrect attitudes (due to the requirements of the job, faulty equipment or developmental or habitual defects of posture) usually leads in time to evidence of local reaction in muscles. Women in industry, unaccustomed to manual work, are rather prone to experience muscular soreness from constant use of a part. Referred pain becomes a later problem. Use of a part is physiologic, overuse is pathologic. Chronic strain leads to muscular fatigue and local accumulation of waste products in the muscles. This sets the stage for painful fibrous sheaths or nodules with resultant referred pain just as described by Dr. Orr.

Much confusion to the patient and travel from doctor to doctor are caused by the tenderness noted in the area of referred pain. The physician concludes erroneously that the pathological condition is located there. The therapy is directed to the peripheral area with no effect. Many urological operations have been done uselessly because of such unexplainable distress due to referred pain. This is because we are accustomed to think only in pain patterns.

I think this paper has been exceptionally worth while and has left us with a great deal of food for thought.

DR. JOHN K. ORMOND (Detroit, Mich.): I should like to ask Dr. Orr a question. Among his cases, in which the pyelograms were normal, were there any in which pain was produced by distension of the pelvis?

DR. LOUIS M. ORR (Orlando, Fla.): In the normal pyelogram, Dr. Ormond, we did find that in each instance by distension of the pelvis we could produce pain very much as they did when they localized pain in relation to true pelvic disease, not ureteral disease.

BILATERAL URETERAL OBSTRUCTION DUE TO ENVELOPMENT AND COMPRESSION BY AN INFLAMMATORY RETROPERITONEAL PROCESS

JOHN K. ORMOND

From the Henry Ford Hospital, Detroit, Michigan

The following 2 cases I deem worthy of presentation to you because not only are they unique in my experience but I have so far been unable to find any similar cases in the literature.

The first case is that of a Greek male whose age was 45 when first seen by us in June 1942. His complaints were substernal pains radiating down the inner surfaces of both arms; low backache of 4 months duration, radiating down both thighs but especially the left; and loss of 10 pounds in weight in the previous 5 months.

There was nothing of special interest in his family and past histories except that his father had died of Bright's disease and his mother was hypertensive.

General physical examination showed as follows: Weight 139½ pounds. Ocular reflexes normal. Tonsils small. Teeth in good repair. No general lymph gland enlargement. Lungs and heart clear to auscultation and percussion. Blood pressure 138/100. No hernia. No abdominal masses or tenderness. No costovertebral tenderness. No abnormalities of bones and joints. Deep reflexes normally obtained. Prostate not unusual. There was a small right hydrocele.

Urine: specific gravity 1.033, no albumin, sugar, or red blood cells, but a few pus cells. Hemoglobin 10.8 gm. per 100 cc. Red blood count 4,320,000, leukocytes 5,800. Wassermann negative.

A complete gastro-intestinal examination disclosed no organic lesion.

An orthopedic consultation was obtained becaused of the backache radiating to the thighs; x-rays showed slight lipping of the tenth and eleventh dorsal vertebrae; the spinal motions were normal; the right leg was a bit shorter than the left and a lift was placed under the right heel. He was put on treatment for angina pectoris.

A few days after the completion of this series of examinations he was admitted to the hospital because of sudden, unheralded and complete anuria of 4 days duration. He was vomiting and his nonprotein nitrogen of the blood was 110 mg. per cent. The next day cystoscopy was done. The bladder was normal and the catheters passed easily up the ureters, meeting no appreciable obstruction and resulting in immediate hydronephrotic drip of clear urine from both pelves. The catheters were left in place and in the first 24 hours the right drained 2000 cc and the left 1000 cc. Pyelograms showed an almost normal right kidney pelvis, the left showing some irregularities suggestive of pyonephrosis. When the catheters were withdrawn there was again complete anuria,

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeous, Absecon, N. J., June 6, 1947.

and they had to be reinserted Transfusions were attempted, but caused cardiac pain and it was deemed best not to repeat the attempt in spite of marked secondary anemia A few days later a right nephrostomy was done No obstruction of the upper ureter was noted and the cortex seemed only a little thinner than normal The nonprotein nitrogen became normal On one occasion urine appeared in the bladder but thereafter none appeared, so left nephrostomy was performed at the end of 2 weeks, and the cortex of the left kidney found to be fairly well preserved At this time he was very anemic, the hemoglobin reading being 7 6 g per 100 cc

The renal function rapidly improved, but not until the ureters were dilated with bulbs 8 on right and 10 on left on two occasions was the ureteral flow reestablished

The patient was sent home voiding normally, and with both nephrostomy wounds closed On October 23, 1942, three months after the onset of anuria, his urine contained pus and marked secondary anemia persisted During the next 3 years he reported for observation and treatment at irregular intervals At first the nephrostomy wounds reopened occasionally, but they remained closed after March 1943, five months after his discharge from the hospital His urine remained infected in spite of the use of sulfa drugs, his anemia improved at first, but after a few months relapsed He continued treatment for angina pectoris, and almost every time he reported to the clinic his ureters were dilated with bougies with bulbs 8 or 10, which passed with ease His course was gradually downhill, the anemia persisting, the urinary infection persisting, and the renal function diminishing

In January 1945 he was admitted to the hospital for penicillin treatment The urine was cloudy with pus, the nonprotein nitrogen was 82 mg per cent, his blood pressure was 175/90 Cultures at various times during the course of his illness had showed staphylococcus, hemolytic streptococcus, and B aerogenes, and the infection had not yielded to the sulfa drugs During this admission he was given 100,000 units of penicillin per day for 3 days, but without effect on the urinary infection

Six months later his hemoglobin showed 7 5 g per 100 cc blood, so he was given transfusions, this time with no reaction and his hemoglobin rose to 10 3 The phenolsulphonphthalein output registered zero in 2 hours In October 1945 catheters were easily run up to the kidney pelvis, the urine contained pus and the indigo carmine did not appear in 14 minutes He was again admitted for transfusions since the hemoglobin had gone back to 7 gm

In February 1946 he was admitted in uremia and with advanced anemia and died Autopsy showed a fibrous retroperitoneal mass covering the promontory of the sacrum and extending up to the kidney The ureters, which were structurally normal and showed no strictures, ran through the lateral margins of this mass, and were enveloped and compressed by it, but not invaded The kidneys were completely destroyed by infection and back pressure I quote from the autopsy report

"The retroperitoneal tissues surrounding the aorta and extending from the kidneys to below the sacral promontory show almost complete replacement with a dense, greyish-white fibrous connective tissue mat. This tissue is 2 cm. in thickness at its thickest point and extends out to and including the ureters.

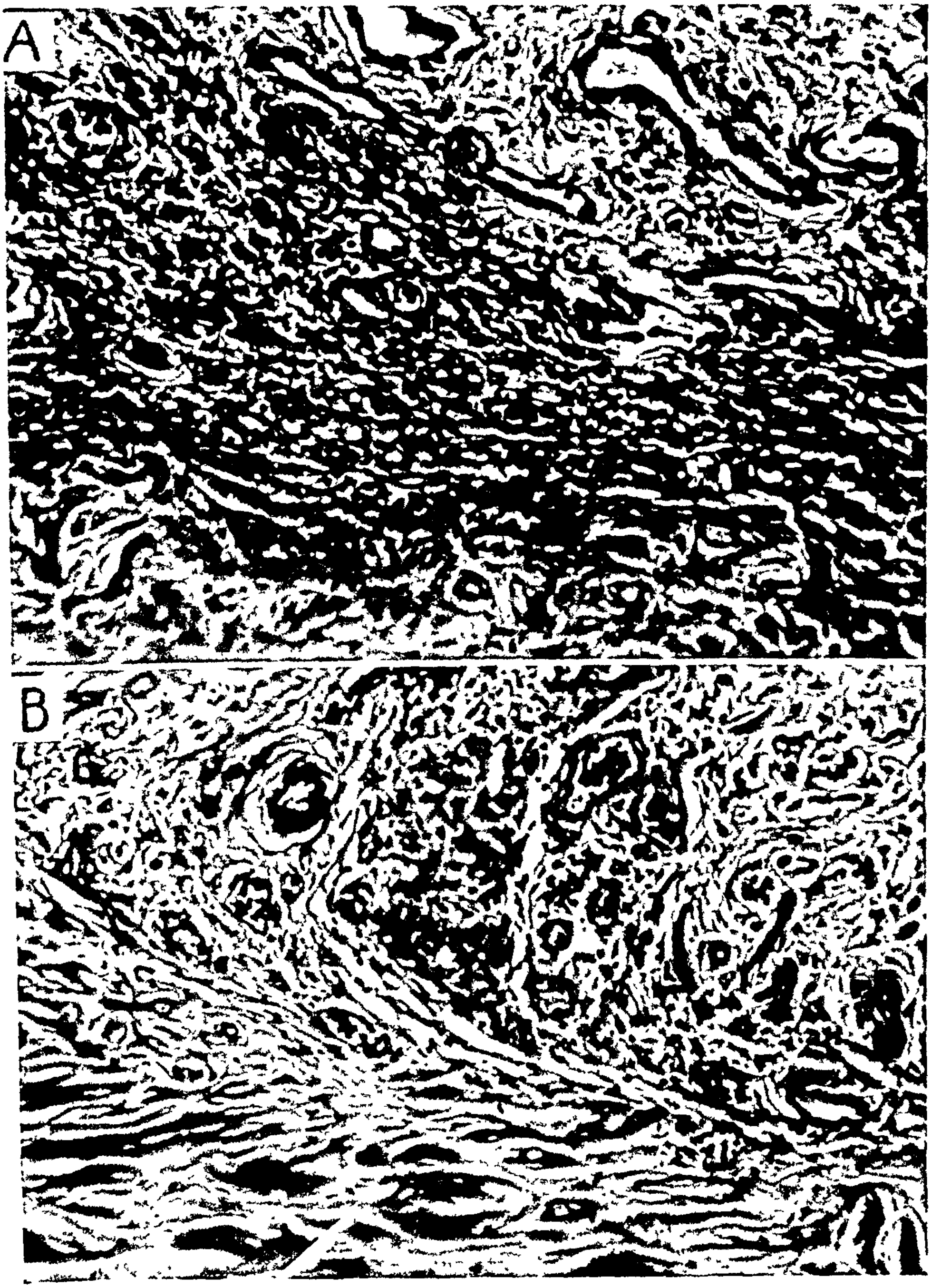

FIG. 1. Case 1. Sections from autopsy specimen of retroperitoneal tissue

The ureters, aorta and vena cava all traverse this dense mass of fibrous tissue which is sufficient to nearly occlude the lumina of the ureters.

"Sections of this dense fibrous mass (figs. 1 and 2) reveal that it is composed entirely of extremely dense bundles of collagen. This tissue is poorly nucleated, but the cells, where seen, are of typical fibrous connective tissue type. This fibrous connective tissue surrounds without invading the large vessels, lymph nodes, nerves and ureters.

"Sections at the edge of this area of fibrosis reveal a rather sharp demarcation, but absolutely no evidence of encapsulation. The cells composing this area of fibrosis are all extremely small and show no evidence of malignancy. In one portion the fibrous tissue is invading the surrounding skeletal muscle, which shows, as previously surrounded muscle is examined, a gradual atrophy and disappearance. This fibrous tissue has no sign of malignant characteristics and has rather the appearance of a keloid."

The second case is that of a man whose age was 43 when he first came under urological observation in January 1946. Previous to this he had been under observation by various divisions of the Henry Ford Hospital over a period of about 22 years, so his past history was well known to us. He was never robust, was always under par, and showed a mild secondary anemia over several years.

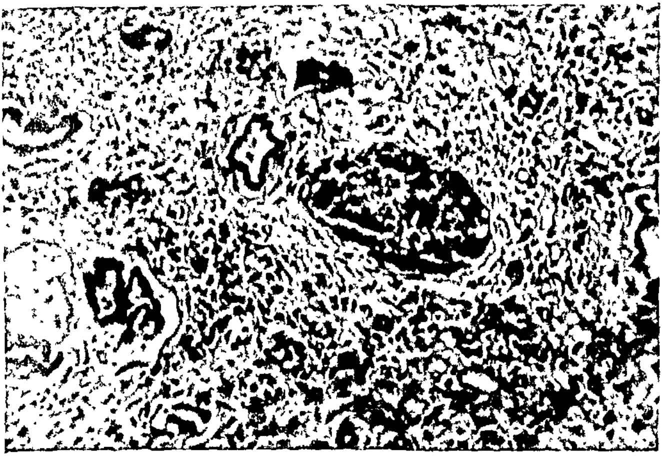

FIG. 2. Case 1. Section from autopsy specimen of retroperitoneal tissue

In 1921 cholecystectomy and appendectomy were performed. Following this he had a wound infection that cleared up in 3 months.

Between 1924 and 1943 he received attention at various times for upper respiratory infections, furuncles in various regions, hypothyroidism, and in 1941 an attack of bacillary dysentery. As this period is reviewed the impression is gained that he was a man rather unusually subject to infections. At no time in this period did the urine show any abnormality and the blood Wassermann test was negative.

In 1943 he first complained of lumbo-sacral backache and late in 1945 the back pain became severe. X-rays showed calcification of the intervertebral disc between the eleventh and twelfth thoracic vertebrae and a number of calcified glands in the right lower abdominal quadrant. There was one large dental abscess.

In January 1946 the back pain increased. Neurological examination gave normal findings, so his back was strapped, but with no relief. At this time he was seen in urological consultation because of the backache associated with ache in the testicles. The urine was clear, of normal specific gravity, and routine examination of the genito-urinary tract gave no indications for more extensive examinations. In February the back pains became so severe as to require Demerol for its relief. At this time the blood showed hemoglobin 11 grams per 100 cc, red cells 3,860,000, leukocytes 8,250; urine, specific gravity 1.032, no albumin or sugar, and no red blood cells or pus cells. An x-ray of the urinary tract showed no abnormality. His pain increased, being worse at night. Barium enema and chest x-rays showed nothing abnormal.

A pantopaque myelogram showed some suggestion of a pressure defect in the region of the third lumbar disc and also in the region of the lumbo-sacral articulation. So on February 15, 1946 a bilateral laminectomy between the third, fourth, and fifth lumbar vertebrae was done. Some extradural adhesions to the lumbar nerves were freed and the presence of some varicosities noted.

It was noted on March 19 that there were no urinary or gastro-intestinal symptoms; that the back symptoms were largely relieved, but that there was pallor, asthenia and no gain in weight. The prostate was again examined but it showed nothing suspicious. On March 25 there was sudden complete urinary suppression, without any pain.

Physical examination showed no general or local lymph gland enlargement; the thyroid was not enlarged; heart and lungs were clear to auscultation and percussion; blood pressure 138/100; no abdominal tenderness or masses; no abnormality noted so far as bones or joints were concerned except the recent operation on the back; deep reflexes were normally obtained. The Wassermann test had always been negative. Catheterization showed no urine in the bladder. Cystoscopy was done and catheters passed up both ureters, finding urine in both pelves. Pyelograms were unsatisfactory, but some dilatation of the pelvis on the left was noted. The catheters were left in place and dripped continuously for some hours. Next day they became plugged and were withdrawn. The one on the right was re-introduced all the way to the pelvis, but that on the left would pass only part way, although urine dropped from it freely. With these catheters in place the nonprotein nitrogen fell in 3 days from 73 mg. per cent to 24 mg. per cent. When the catheters were withdrawn no urine reached the bladder and it was necessary to re-introduce them.

Because of his anemia and of the puzzling character of his course in the past, it was suspected that the ureters might be involved in some malignant process, and the decision was made to explore the abdomen.

On April 4, 1946 a right para-median lower abdominal incision was made. The peritoneal surfaces were smooth, the kidneys felt normal, the liver was not enlarged and no nodules were felt on its surface The gallbladder had been previously removed and there were numerous adhesions in this region A retroperitoneal flat mass with indistinct lateral margins was felt covering the promontory of the sacrum A bit of this was removed for biopsy and frozen section showed it to be inflammatory in nature I quote from the pathological report

"Sections of the retroperitoneal tissue reveal alternating areas of dense, fibrous, connective tissue and fat (fig 3) Throughout the entire sections examined is a diffuse infiltration of small, round and wandering cells, occasional eosinophils and polymorphonuclear leukocytes In some instances the lymphatic cells are collected into small follicles Considerable fibroblastic activity

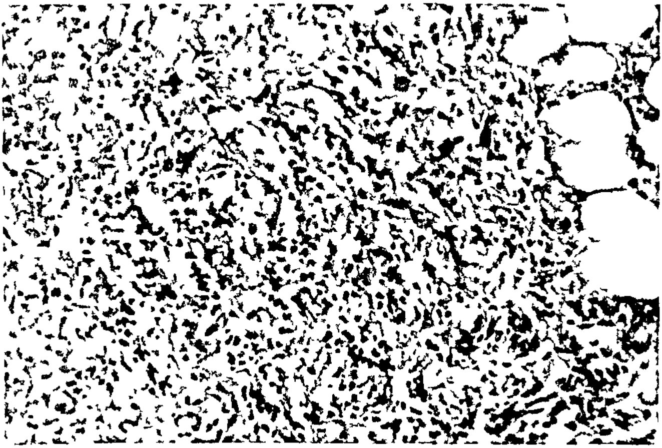

FIG 3 Case 2 Section from biopsy of retroperitoneal tissue

is seen but no abscesses are present and there is no evidence of a specific etiology There is no microscopic evidence of a neoplastic process"

The ureters were located below this mass, traced up, and found to pass through this tissue near its lateral margins Both ureters were dissected entirely free from this enveloping tissue and seemed entirely normal They were left free in the abdominal cavity, no attempt being made to cover them with peritoneum The abdominal wound was closed with drainage because of oozing The ureteral catheters were removed in the next 2 days Wound healing and convalescence were uneventful and there has been free and normal urination ever since He was given deep x-ray therapy directed at the inflammatory mass described above, and his health has improved remarkably He is no longer anemic, has put on weight, is working regularly and feels the best he has felt in several years We have followed his kidney condition by means of the phenolsulphonphthalein test and excretory urography The phenolsulphonphthalein output has been normal and his last urogram showed no evidence of ureteral obstruction.

On May 13, 1947 a cystoscopic examination was done. The bladder seemed everywhere normal. Indigo carmine appeared from the left ureteral orifice in 3 minutes and from the right a few seconds later. A catheter was easily passed up the left ureter, but it could not be engaged in the right ureteral orifice.

On May 19, 1947 a phenolsulphonphthalein test showed 60 per cent in the first hour and urinalysis showed as follows: specific gravity 1.024, no albumin or sugar, no pus cells, occasional red blood cell.

DISCUSSION

Here are reported two instances of ureteral compression due to envelopment by a retroperitoneal, non-malignant mass. In both instances there was sudden, complete anuria. In both there was a preceding period of reduced health, unexplained anemia, and backache. In neither had there been any preceding urinary disturbance. The microscopic appearance of the retroperitoneal tissue in the 2 cases shows some similarity or relationship between them. In the second case the tissue is obviously inflammatory in origin and fairly recent or acute. In the other it could well be in the nature of scar, or the result of past inflammations. In other words, it is conceivable that the tissue from the first case represents a later stage of a process of which the tissue of the second case represents an earlier stage and this would be in accord with the different periods during which each was observed.

We were much puzzled by the course of events in the first case. We could not detect any ureteral strictures. Ureteral catheterization was always easy, yet there was pelvic retention of urine, and persistent and increasing pyelonephritis, and renal deterioration.

As I look back on it, it seems that we were rather stupid not to recognize that there was ureteral obstruction of extra-ureteral origin and that we should have explored the abdomen. It seems likely that had we done so and freed the ureters as we did in the second case, the result would have been very different.

It seems highly probable that the backache in both instances was due to the inflammatory retroperitoneal activity, and it seems possible that the reference of that ache, in one case to the thighs and in the other to the testes, was due to irritation of the ureters as they became involved in this enveloping and compressing tissue.

We have no theories to offer as to the genesis or development of these inflammatory masses or processes. It is possible that they have something to do with the lymph glands of this region, but there is in neither case any history of preceding infection of the genitalia, legs, urinary tract, or of any evidence of diverticulitis of the bowel. The possibility of brucellosis has been suggested. This could not be proved now and was not suspected at the time. I do not know whether this is a new observation or not. It is certainly new to me and to our pathological department but it is entirely beyond the bounds of possibility that there have been only two instances of this condition.

Since the process is not invasive it would probably make its presence known as it developed and spread only by the result of compression of the neighboring structures as they became enveloped by it. Of these structures the ureters would be most apt to give unmistakable evidence of their compression.

Both these patients had severe backache, which may be attributable to this inflammatory process, but obscure backaches are common and rarely demand radical or emergency treatment, while complete obstruction of the ureters urgently demands attention.

In a thorough review of the urological literature I have not found similar cases reported. If I have overlooked any reports or if any of you have seen such cases, I shall be much interested to learn of them.

ECTOPIC INSERTION OF THE URETER AS A CAUSE OF URINARY DRIBBLING; COMPLETE CURE BY HEMINEPHRECTOMY

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Ectopic insertion of the ureter is encountered only occasionally, even on a busy urological service. When it produces a chain of symptoms such as is about to be described, complete cure can be effected in an almost dramatic fashion. Our purpose is to focus attention on the existence of this anomaly to facilitate prompt recognition of cases similar to this one. When this condition is recognized, the treatment is evident and the results of proper surgery restore these patients from lives of embarrassment and seclusion to their proper places as useful, unself-conscious members of society.

CASE REPORT

A 6½ year old white schoolgirl was admitted to the urological service of the Long Island College Hospital on November 19, 1946. According to her mother, since birth the child had continually dribbled urine, both during the day and during the night. In addition to the fact that the child was always wet, the mother stated that the patient voided at normal intervals and was apparently in complete control of urination.

Several physicians treated her for enuresis, with no result. She continued to be wet night and day and also continued to void apparently normally. Her life at home became regulated on the basis that her ailment was hopeless. The furniture in the house was covered with rubber pads. She, herself, continued to wear diapers at an age when she was beginning to attend school. Her life at school was rather miserable because of the inconsiderate attitude and the remarks of the other children, with the result that she became self-conscious and avoided attending school. She was considered to be neurotic and a psychiatric problem, and her family had begun to believe that all that could be done on their part to meet the problem was to appreciate the fact that it existed and that they and the child must become reconciled to it. They decided to consult a pediatrician, in a last effort to determine if anything could be done for the child. This physician was the first to recognize that a complete urological survey was indicated and, accordingly, referred the case to the urological service.

Preliminary cystoscopy and retrograde pyelogram done prior to admission seemed to be normal (fig. 1, *A*). However, because of the classical history of dribbling and apparently normal bladder function, an ectopic ureteral orifice was strongly suspected. On the day of admission, an intravenous pyelogram was done which made the diagnosis (fig. 1, *B*). The report of this pyelogram was as follows: "Normally functioning kidneys. On the right side there is an anomalous arrangement with two pelves. The superior pelvis shows considerable hydronephrosis. Only the ureter leading from the lower pole is visualized. The ureter from the upper pelvis is not seen."

Cystoscopy was repeated on November 21, 1946, and diligent search was made for ectopic orifices. Catheters were inserted into each normal orifice and intravenous indigo carmine was administered. A blue discoloration was seen about the vagina, but no point of origin of the dye was definitely visualized.

Physical examination was negative in all respects other than as described. Urinalysis was negative except for occasional pus cells in the voided specimen. Blood chemistry was normal.

Operation (November 25, 1946): The usual right loin incision was made and the kidney was exposed. A single kidney was found, which appeared normal except at the upper pole which appeared slightly wider than normal and flattened at its apex. A dilated thickened ureter was found leading from the upper pole which had the appearance of being chronically infected. It was traced distally as far as possible and the thickening and dilatation were present for the entire length that was exposed. A ureter that appeared normal in all respects was found leading from the remainder of the kidney.

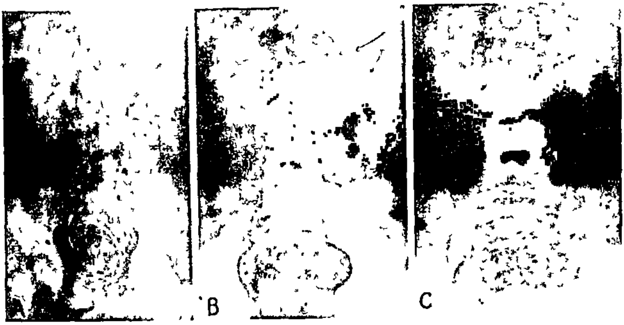

FIG. 1. *A*, Preoperative retrograde pyelogram *B*, Preoperative intravenous pyelogram. *Note double kidney pelvis on right* *C*, *Postoperative intravenous pyelogram. Compare with* B.

Separate blood supplies were seen entering the kidney, one to the upper portion and one to the lower. Since the upper portion of the kidney and the upper ureter were the ones considered to be abnormal, the blood supply to the upper portion was clamped. Immediate cyanosis of the upper pole was noted and a definite line of demarcation was noted at the junction of the upper and middle thirds of the kidney. Using this line of demarcation as a guide, the upper pole was excised as a wedge shaped piece of tissue The thickened ureter was clamped, cut and tied as far distally as was accessible. The blood supply was tied in the usual manner. Minimal bleeding followed the excision of the upper portion of the kidney. The raw surface was covered with Oxycel and the kidney wound was sutured with atraumatic mattress sutures, using pieces of fat anchored between the sutures and the kidney surface. The wound was closed with drainage.

Five hours postoperatively, the patient voided. There was no evidence of dribbling at that time and there has been none since. The postoperative course was uneventful from the surgical standpoint. The drain was removed on the third postoperative day and all sutures were out by the eighth postoperative day. Convalescence was prolonged slightly by the development of an upper respiratory infection on the ninth postoperative day. This subsided without complication. An intravenous pyelogram showed normally functioning kidneys and no evidence of the anomaly which existed prior to operation (see fig. 1, *C*).

The pathologist's report on the portion of kidney excised was that there was nothing abnormal histologically. The ureter, however, was dilated and its walls were markedly thickened. Diagnosis was made of chronic ureteritis.

From the time of operation until the present date, the patient has had no further complaint of dribbling. Her mental outlook, her attitude toward school, her associations with other children, have improved considerably and she is now a normal individual.

REPORT OF TWO CASES OF CARCINOMA OF THE URETER, DISCUSSION OF THE PATHOGENESIS OF URINARY TRACT TUMORS

THOMAS GUALTIERI JAMES J HAYES AND ABRAHAM D SEGAL

The clinical aspects of ureteral neoplasms have been adequately covered in the recent contributions to the literature by Higgins, Foord and Ferrier, Cook and Counseller, W W Scott, Jaffee and Mendillo, Counseller, Cook and Seefeld, Lazarus and Marks, and others The subject has been reviewed in a most thorough fashion, individual cases have been analyzed and appraised, and the notable achievement of bringing about an awareness on the part of the surgeon as to the not too infrequent occurrence of these growths has been attained An inkling into the progress made in the past half century may be had when one notes that Van Buren and Keyes in their textbook on Genito Urinary Diseases written in 1874, devoted less than 1 page to diseases of the ureter and we find absolutely no mention of ureteral tumors In contrast, Lowsley and Kirwin set aside 5 full pages in their textbook for a discussion of ureteral tumors alone

Two cases of carcinoma of the ureter which presented themselves in recent years at the Coney Island Hospital are presented, and in addition an attempt will be made to crystallize the essential knowledge at hand anent the subject of the pathogenesis of urinary tract epithelial tumors Certain personal convictions and preferences are offered for consideration and appraisal of worth

In addition to our 2 cases there are 3 others in the current literature, one each by Barney, Schulz and Castleman, Ibanez, and de la Pena and de la Pena These 5 cases, added to the 191 reviewed by Counseller, Cook and Seefeld, bring the total number of reported cases of carcinoma of the ureter to 196

CASE REPORTS

Case 1 I W , a white male 66 years of age, was admitted December 7, 1939 to the Coney Island Hospital with a history of loss of 15 pounds in weight and pain in the left lower abdomen for a period of 5 weeks He had a suprapubic prostatectomy 1 year previously following an episode of acute urinary retention, and benign hypertrophy of the prostate was reported Physical examination revealed a large mass in the left loin which extended anteriorly and almost filled the left side of the abdomen

Urine showed 2+ albumin, 40 to 50 leucocytes and 8 to 10 erythrocytes per high power field Urine culture showed Friedlander's bacillus

A plain x ray showed the right kidney normal and a large mass in the left kidney region Intravenous pyelogram showed a normal functioning right kidney and no dye in the left side On cystoscopic examination catheters of different sizes could not be passed beyond 15 cm on the left side While changing catheters a cast of muco purulent material and sanguineous debris was dislodged Dye injected into a catheter within the ureter at this level revealed a collection of opaque solution in the kidney region, apparently in a large irregular cavity. The ureter was widened and incompletely filled. There appeared to be numerous small filling defects in the dilated lower extremity of the ureter (fig. 1).

The diagnosis was 1) perinephric abscess, 2) pyonephrosis left, secondary to carcinoma of ureter.

Operation (December 11, 1939): Under local anesthesia an incision 4 inches long was made in the left costovertebral region and about 2 liters of foul smelling, thick, purulent material was evacuated. Two Penrose drains were inserted and the cavity was packed with iodoform gauze, which was gradually removed.

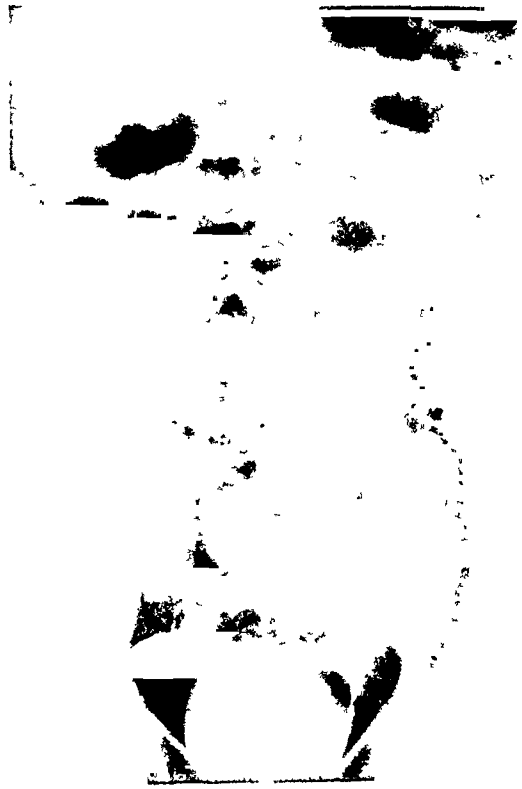

FIG. 1. Note irregular mass of dye in left renal cavity. Left lower ureter, stipple effect of incomplete filling.

The patient's general condition improved. In view of his age it was decided to do a nephrectomy and ureterectomy in 2 stages.

Operation (January 31, 1940): The scar in the left loin was excised and the incision lengthened anteriorly 4 inches, exposing a moderately enlarged kidney with nodular areas which were firmly adherent to peritoneum. The ureter was markedly redundant and thickened to about 5 times normal size. It was also nodular in consistency throughout its entire length. It was excised as low as possible (at the midureter) and tied off with a chromic No. 2 suture following cauterization at line of severance. The end of the suture was allowed to extrude through the lower end of the wound. A Penrose drain was threaded over the retained lower portion of the ureter and end of the drain allowed to come out through lower end of incision. The pedicle was clamped and the kidney excised in the usual manner. Closure was in layers with chromic for muscle and fascia, interrupted black silk for skin.

Convalescence was slow and 4 weeks later the secondary operation was performed. An incision 5 inches long was made in the left lower abdomen, extending from the suprapubic area towards the anterior superior spine. This was deepened through the muscles to the peritoneum which was retracted, exposing the remainder of the ureter still encased in the Penrose drain. Further dissection presented the left bladder wall from the dome to the ureterovesical junction. The ureter was excised with a conical cuff 5 cm. in diameter of vesical tissue around the ureteral orifice. The bladder was closed with interrupted chromic sutures. A Pezzar catheter was inserted through a stab wound in the dome of the bladder and closed with a purse-string suture. Penrose drains were inserted behind the bladder and in the space of Retzius. The drains were removed on the tenth day and the suprapubic tube on the twelfth day. The patient then began voiding spontaneously. Both the suprapubic and nephrectomy wounds were well healed at the time of discharge from the hospital on April 14, 1940.

Pathological report (Dr. H. Fink): "Kidney and upper ureter: specimen consists of left kidney, measuring 15 by 8 by 7 cm. and portion of attached ureter, weighing 335 gm. The attached portion of ureter is 10 cm. in length. There is a considerable amount of perirenal fat. On section the pelvis and major calyces are enormously dilated, containing a dirty brown purulent material. The pelvis is markedly dilated and there is noted at the ureteropelvic region a fungating papillary mass which appears to have its origin in the attached portion of ureter which contained the same type of growth (fig. 2).

"Microscopic sections from pelviureteral and ureteral masses show a papillary growth of irregularly cuboidal and polygonal cells with large vesicular nuclei and enormous nucleoli. Throughout there are mitotic figures. The stalk is thin, vascularized and in some areas shows invasion. At one point there is a central blood vessel which shows invasion of the adventitia but the inner coats are intact."

"Sections of the kidney proper show in several areas, numerous needlelike spaces surrounded by an enormous number of foreign body giant cells. In addition there are large vacuolated cells with small nuclei. In the peripheral zone there are remnants of urinary tubules and numerous completely hyalinized glomeruli. Diagnosis: Papillary carcinoma of the ureter; pyonephrosis; xanthomatosis of the kidney with foreign body reaction.

"Lower ureter and portion of bladder: Specimen consists of a portion of ureter measuring 15 cm. in length and 1.5 cm. in diameter. Beginning at the proximal end, and extending for a distance of 7 cm., the mucosa is rough, raised, and nodular with numerous areas of hemorrhage and ulcerations. The circumference of this area is 2.2 cm. There is moderate thickening of the wall which measures 3 mm. in thickness. Distal to this region the mucosa is pearly gray in color and smooth." (See fig. 3.) "Microscopic sections show irregular areas of ulceration and necrosis of ureteral mucosa. In some areas this is replaced by a pyogenic membrane with innumerable polymorphonuclear leukocytes and newly formed pushed cephalad well into the left lumbar gutter. The bladder defect was closed with continuous No. 1 chromic suture and a drain placed in the retrovesical space. The cystostomy wound was treated and closed in the usual manner.

The patient was turned on his right side and a left loin incision was made. After entering the fascia of Gerota the twelfth rib was dislocated in order to facilitate the mobilization of the kidney. The upper ureter was identified and freed down to the pelvic brim. It was now possible to draw the entire ureter and mass along with its Penrose drain covering out through the loin incision. A rapid nephrectomy followed. Two Penrose drains were inserted and closure was carried out in the usual way. The patient was returned to the ward in good condition. Convalescence was not unusual except for a low grade temperature for a period of 3 weeks. This subsided with antibiotic therapy. All packings and drains were removed in 1 week and all sutures were out by the tenth postoperative day. The suprapubic tube was withdrawn on the twenty-first day and all wounds were healed in 1 month. The patient was discharged February 14, 1946.

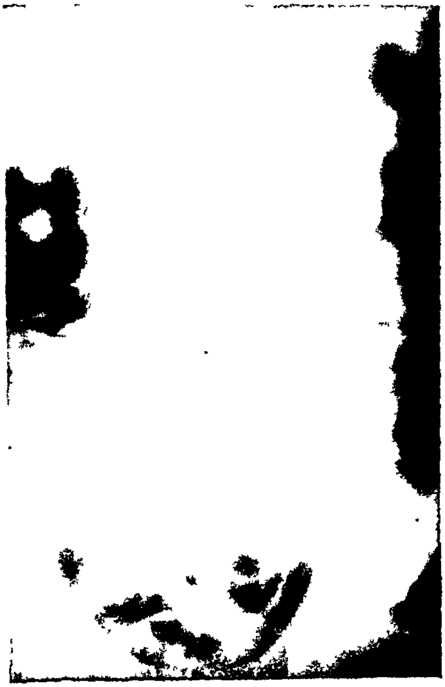

FIG. 4. Hydronephrosis; dilated and redundant ureter. Lower ureter shows irregular filling defect with inverted meniscus at abrupt cessation of continuity of dye.

Pathological report (Dr. I. Rudolph): "The specimen weighs 150 gm. and consists of kidney with attached total ureter and a portion of bladder attached to the ureter. The kidney measures 18.5 cm. in length by 7.5 cm. by 5 cm. The capsule strips with ease leaving a smooth cortical surface.

"On section the cortex is of average width and is clearly demarcated from the medullary portion. The pelvis is dilated to 4.5 cm. in width and there is a marked increase of pelvic fat.

"The attached ureter measures 32 cm. in length, is dilated and measures 2.5 cm. in circumference. In the distal portion of the ureter, 2 cm. from its attachment to the bladder, there is a bulbous dilatation measuring 4 5 cm in circumference On section of the ureter, the lumen is patent throughout up to the point of the bulbous dilatation, here attached to the wall of the ureter, is a mass measuring 3 25 cm in length and 1 cm in diameter This mass almost completely occludes the lumen of the ureter It is grayish brown in color, soft in consistency On section it shows numerous hemorrhagic areas diffusely distributed throughout The attached portion of the bladder measures 3 cm in diameter (fig 5) "Micro-

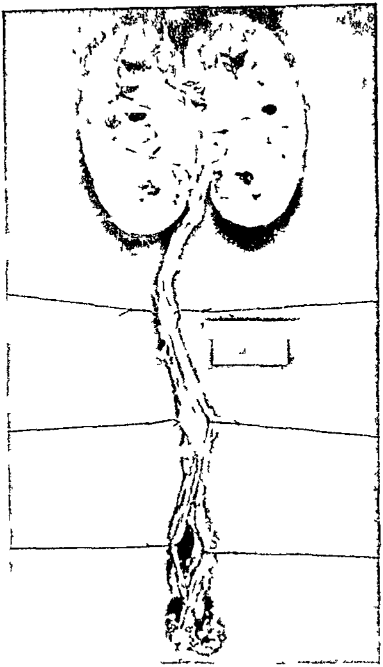

Fig 5 Kidney ureter and cuff of bladder Hemorrhagic neoplasm 4 cm above uretero vesical junction Hydronephrosis not so marked as pyelogram would suggest

scopic sections from the ureter show marked cellular activity The cells show papillary arrangement The stalks are thin There is marked cellular infiltration The nuclei show evidence of mitotic divisions and there is moderate hyperchromatism of nuclear material Other areas show hemorrhagic degeneration There are a few blood vessels present which are intensely engorged There is a round cell infiltration of the interstitial tissue and a moderate perivascular round cell cuffing present (fig 6)

"Kidney presents diffuse changes The glomerular tufts show some fibrosis and hyalinization. The tubules show widespread diffuse, cloudy swelling and in some areas a desquamation of the epithelium. The interstitium shows some areas with round cells and numerous polymorphonuclear leukocytes. The blood vessels show diffuse hyperplastic sclerosis, some being moderately engorged.

"Sections from the pelvis of the kidney present a diffuse inflammatory process with some round cells; numerous polymorphonuclear leukocytes and an occasional plasma cell. Occasionally there is noted a follicular collection of small round cells.

"Sections of bladder wall show a diffuse round cell infiltration with numerous polymorphonuclear leukocytes. No evidence of malignant infiltration is noted. Diagnosis: Papillary carcinoma of the ureter; chronic pyelonephritis; and hydronephrosis.

The patient was followed for 1 year and at no time was there any sign or symptom of recurrence. Cystoscopy 6 months postoperative revealed a normal bladder.

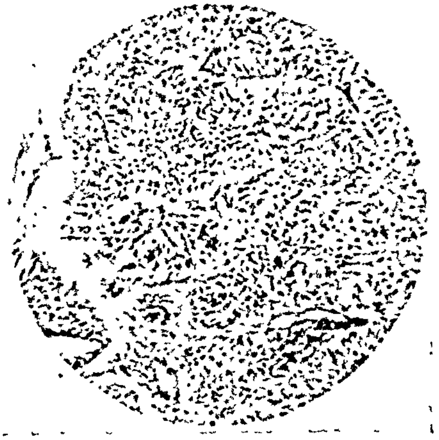

Fig. 6. Showing papillary as well as solid type of cytoarchitecture

Nine months postoperative the patient suffered an attack of coronary thrombosis and was bedridden for 3 weeks. At this time x-ray and blood studies were normal.

He died suddenly following a second coronary attack 1 year after his original hospital admission. Unfortunately, an autopsy was not obtained.

PATHOGENESIS

Ureteral epithelial tumors are histologically and clinically akin to those arising from the mucosa of the kidney pelvis and bladder. All these tumors exhibit a similar behavior pattern which is characterized by two outstanding features: a marked tendency to "recurrence" and a propensity to multiplicity. Actually, as we shall see further on, these two features are manifestations of one property i.e. a simultaneous or consecutive multiplicity. Whatever individual differences are encountered are more apparent than real and may be accounted for on a basis of anatomical structural characteristics at the three levels in the urinary tract. For example, a neoplasm of the kidney pelvis is very apt to invade the nearby renal vein; a ureteral tumor will metastasize comparatively early because of the thin wall of the ureter and its rich blood supply. The simultaneous involvement by neoplastic growth of kidney pelvis, ureter and bladder has given rise to a good deal of speculation among numerous observers so that in time three hypotheses have emerged: 1) implantation by surface extension (Albarran and Imbert, Cabot and Allen, etc.); 2) extension by lymphatics (Kimball and Ferriss, Saltzstein and Beaver, etc.); 3) multicentric origin (Ewing, Johnson, Caulk). The latter hypothesis has been rather generally accepted, especially since it has been bolstered by important substantiation in the more recent work in this field. We are of the opinion that the concept of the multicentricity of origin offers the only satisfactory explanation of the distinctive behavior of urinary tract epithelial tumors.

Recently, Melicow has called attention to certain embryological, histological and clinical evidence in favor of including kidney pelvis tumors with those of the ureter, bladder and urethra, with the idea of separating them, as a group, from kidney parenchymal tumors. He further proposes the designation "urothelium" for the epithelial lining of the urinary tract, and because of its uniform and characteristic structure, distinguishes it from the epidermis of the skin and the mucous membrane of the gastro-intestinal tract. We fully concur in this newer concept and regard its general acceptance as a necessary prerequisite to the fuller understanding of the recent observations in the pathogenesis of urinary tract tumors.

The epic-making discoveries of Yamagina and Ichikawa in 1915 dealing with the deliberate production of skin cancer in rabbits following the application of tar, served as an impetus to renewed activity and enthusiasm among the numerous workers in the field of cancer. In 1922, Gay, Hueper, and Ferguson demonstrated that certain chemicals (benzidine and alpha- and beta-naphthylamine) employed in the manufacture of aniline dyes were directly responsible for the high incidence of bladder tumors among workers. These chemically-induced tumors appeared identical in all respects with their spontaneous counterparts. They may be single or multiple, benign or malignant, and they are all epithelial in origin. Of especial significance was the decided discrepancy in the relative incidence of benign and malignant growths encountered by separate investigators. Figures are available to show a higher percentage of malignant tumors occurring in those series of cases where cystoscopic investigation was delayed or postponed. Thus it is evident that the element of time is concerned with the "transition" from benignity to malignancy.

Extended investigation into the problem of chemical carcinogens led to the synthesis of certain hydrocarbons represented by the benzpyrene, benzanthracene and cholanthrene groups, the composition of which is characterized by the presence of the so-called "phenanthrene nucleus" (fig. 7). These groups are demonstrably carcinogenic, which property was attributed to the "nucleus". Significantly enough, this very phenanthrene base is found in the composition of certain normal body constituents, notably cholic acid, the sterols, and the sex hormones; thus establishing a definite structural relationship. This naturally led to the hypothesis that any disorder in tissue metabolism might conceivably lead to the endogenous synthesis of carcinogens

Davis recently reviewed the tremendous experimental achievements in this field, especially by the London and Harvard groups, and directs attention to the multiplicity and variety of proven and suspected carcinogenic agents.

A common characteristic of carcinogenic agents of whatever type is an inherent capacity to set up a special kind of chemico-biologic irritation which, under propitious conditions and after an unpredictable lapse of time, will produce a cancer growth.

Carcinogens, then, may be derived from exogenous sources (ingestion, respiration, skin contact, etc.) or from endogenous foci (synthesized products of abnormal metabolism, bacterial excretions, mutation forms, virus forms, etc.).

It would appear that the accumulated evidence in favor of chemical carcinogenesis is both impressive and convincing.

The urothelium, the receptor, resistance and susceptibility. The urothelium is in the main a protective lining, and serves as a barrier against possible deleterious action of certain normal and abnormal urinary constituents. Under ordinary circumstances it manifests neither absorptive nor secretory powers. However, because of the unique rôle assumed by the urinary tract in extruding accumulated urinary irritants of one kind and another, and because of its notorious susceptibility to infection (due to a tremendously high incidence of congenital anomalies, a tendency to obstruction, and proximity to the rectum), it is probable that in most instances the urothelium is unable to cope with an abnormal situation but rather is more vulnerable than ordinarily suspected. If such is the case, we should expect an epithelial reaction commensurate with the type and persistance of the stimulus. Actually, histological evidence is at hand indicating certain pathological changes pointing to an epithelial "unrest," probably as a result of a biologico-chemical irritation due to chronic infection, trauma, etc.

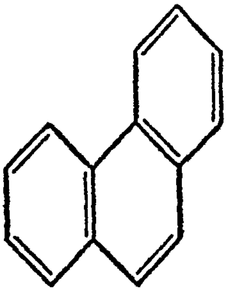

FIG. 7. Phenanthrene is isomeric with anthracene, differing by asymmetry of position of two lateral benzene rings.

Von Brunn, as early as 1893, described unique collections of epithelial cells in the submucosa of the kidney pelvis, ureter and bladder, which he looked upon as arising from an infolding of segments of the epithelium which eventually become pinched off from the parent epithelium. In 1906 Herxheimer found von Brunn "cell nests" in 11 of 29 case studies (none were younger than 2 years of age). Morse in 125 consecutive post-mortem examinations was able to demonstrate epithelial buds or cell nests in 108 (86 per cent), and noted associated chronic inflammatory changes (lymphocytic infiltration, fibrous tissue proliferation and new capillary formation) in 63 of these (58 per cent). In addition, sections taken at different levels in 25 cases revealed cell nests present in the kidney pelvis in 10, in the upper ureter in 15, in the lower ureter in 7, and in the bladder in 12 cases. Bothe likewise discovered the presence of cell nests in 38 of 54 postmortem specimens.

Since some of these sections were indistinguishable from the picture of early malignancy and since these buds were identified as consisting of a transitional type cell rather *immature* and *incompletely differentiated*, the possible rôle of these cell nests as forerunners of carcinoma was envisaged. Thus Patch and Rhea and also Stirling and Ash were inclined to believe that, through a process of evolution of metaplasia, von Brunn nests could be the basis for cystitis cystica or cystitis glandularis and in time adenocarcinoma. Bothe suggested that these immature buds may be the specific tissue susceptible to activation by chemical carcinogens. He believes with Hinman that these cell groups are in effect mucous membrane crypts rather than developmental inclusions and may be due to underlying inflammation. In 12 surgical specimens (4 carcinomas of the kidney pelvis, 7 of the ureter and 1 of the bladder) sections adjacent and also distant to the primary growth were studied by Bothe. No malignancy could be demonstrated but significant were the following pathological changes encountered: 1) a subcutaneous hyperemia and round cell infiltration in some areas, associated in many places with epithelial digitations (not unlike the picture described by Gay in aniline bladders); 2) islands of epithelial cells in the submucosa in other areas.

The "chronic proliferative" lesions of the urinary tract have been grouped as such by Stirling and Ash, and include such clinical entities as cystitis cystica, cystitis granulosa, cystitis glandularis, benign glandular proliferation, hyperplasia of Albarran's glands and cystic adenoma. Hinman and Cordonnier have attempted a classification of these pathological processes. Patch and Rhea consider them metaplastic changes resulting from chronic irritation and infection.

Whether these lesions represent an ultimate specific individual response to abnormal stimuli or rather had better be considered definite progressive phases of one chemico-biological mechanism and therefore essentially precancerous, is not as yet entirely clear. Whether a cancer develops immediately from a cell nest or achieves its final evolution by way of one or more metaplastic phases, must remain in the realm of speculation for the time being. In any case, the positive evidence points directly to von Brunn's cell nests as the basic "nuclei" from which the various familiar urinary tract excrescences and cancer itself develop. In addition, the hypothesis of the multicentric origin of tumors of the urinary tract appears to be incontrovertibly substantiated.

Mechanism of cancerogenesis, a chemico-biological catalyst-enzyme function. The exact nature of the mechanism of urinary tract tumor formation must remain, as of today, more or less a mystery. Yet the facts which have been adduced so far would seem to point the way to a satisfactory working hypothesis, one better calculated to ascertain prognosis and indicate treatment.

We must believe that this mechanism is fundamentally chemico-biologic in nature; that the presenting neoplasm is merely one outward manifestation of an extremely intricate process or series of processes and not its final consummation these tumors with subsequent clinical behavior has led to classifying them according to gross and microscopic structure and various criteria for malignancy have been determined.

Whereas, in the main, a seemingly satisfactory working method has evolved, there has been no little confusion created among the various investigators, arising from their own individual differences in viewpoint, and from personal preferences and opinions. A lack of standardization and a muddled terminology have contributed to the prevailing confusion. The surgeon, as it were, has been buffeted about by the pathologist on the one hand and the patient with his tumor on the other.

An examination of the typical classifications in use today will bear this out.

Ewing utilized 4 general headings in classifying urinary tract tumors: 1) papilloma, benign, 2) papilloma, malignant, 3) squamous cell carcinoma, and 4) alveolar carcinoma, solid. Elsewhere he indicts certain benign appearing papillomas as potentially malignant; also he finds that certain malignant papillomas may infiltrate. There appears to be no distinct line of demarcation between the several types described in this classification.

The gross classification into the papillary and the non-papillary has been complemented by Broders' microscopic sorting and represents, with minor variations and qualifications here and there, a widely employed method of evaluating these tumors. It has been adopted by the Bladder Tumor Registry, Dart, Ash, Scott, Melicow, and others all endeavoring to correlate the gross and microscopic appearance of the growth with its clinical behavior.

Gay classified his aniline tumors solely on a basis of cell structure, and not on cystoscopic appearance, size, or number of growths.

Jolly describes 3 types of carcinoma: 1) the papillary, 2) the squamous with cell nests and cornifying epithelium, 3) the anaplastic.

McDonald and Priestley examined 75 tumors of the kidney pelvis at the Mayo Clinic and found: 1) 27 cases of papillary carcinoma with no infiltration, 2) 25 cases of papillary carcinoma with infiltration, 3) 23 cases of infiltrating carcinoma.

Jewett recognizes 3 types: 1) papillary carcinoma, 2) epidermoid carcinoma, and 3) intermediate forms.

Broders lays emphasis on microscopy and outlines 3 principles in the gradation of urinary tract epithelial tumors.

If we accept the concept of urinary tract pathogenesis as a dynamic mechanism, continuous and progressive, and essentially reversible, we must judge Broders' method inadequate and possibly inapplicable in the case of urinary tract tumors, since the given microscopic picture represents one fleeting phase of a complex process. Also it is bound to recognize several grades of malignancy in the same tumor (Jewett) in most instances. Further, when employed for purposes of prognostication it is of limited value, in spite of its apparent servicibility. Experience has demonstrated over and over again that, by and large, these tumors do not behave clinically as a grade 1 or 3 etc. but instead are notoriously elusive and unpredictable. This was most forcibly illustrated by the case of Rathbun, in which a very small bladder growth metastasized widely and rapidly very early.

Recently Colby and Sniffen have attempted to correlate the varying histologic patterns with the differences in response to the 1200 kilo-volt unit. Had results warranted it, a classification might be possible using response to x-ray therapy as a criterion. However, results demonstrated the papillary and the non-papillary as responding equally well (or poorly) to external radiation.

Scott cites no less than 22 terms employed by as many pathologists in designating the 182 ureteral cancers found in the literature.

Aside from the typically structural classifications, some pathologists have been content with designating all these tumors as epitheliomas and a rough classification according to clinical behavior formulated. Thus Boyd considers the surgeon's point of view more important than microscopy in ascertaining prognosis. Factors noted are the age, duration and size of the tumor, rate of growth, presence of metastases, and the general appearance of the patient. Rather than make histopathology a basis for prognosis, Boyd would employ it in determining radiosensitivity.

Certainly the degree of malignancy of a given growth cannot be judged with any measure of accuracy or confidence by any of the present day standards or criteria. A classification, from the surgeon's viewpoint at least, can be of real value only insofar as it sharply defines the malignancy or benignity of the lesion.

Besides the usual criteria for appraising malignancy (metastases and infiltration), the urinary tract tumor is considered malignant by us because of its propensity for multiplicity, whether it be simultaneous or consecutive. That this property is, sui generis, a manifestation of malignancy should be clear. Conversely, multiplicity cannot possibly be a sign of benignity since the clinical criterion for benignity is simply one—a lesion amenable to complete, conclusive and irrefutable *cure*. (In passing, it might be said that there has been so much emphasis on achieving 5 year cures per se in the past that permanent cure itself has been temporarily lost sight of.)

Taylor suggests: "It is doubtful whether we should ever consider a papilloma benign from a clinical standpoint." Ewing comments: "While the course of these tumors is usually benign, not a few of them have recurred in malignant form—." Counseller, Cook and Seefeld especially emphasize the danger involved in referring to "benign" papillomas as "they are not benign either pathologically or clinically and must be considered as malignant lesions." If we recall the mechanism of carcinogenesis, we must conclude that all urinary tract tumors are malignant. We prefer to use the term eventually malignant in place of the equivocal designation, potentially malignant, for those growths which are seemingly less active than others. Further, we propose that these tumors be evaluated in terms of clinical activity rather than by structural gradation. Finally we feel that an all inclusive descriptive term, indicative of known etiologic factors exclusively found in the urinary tract, should be employed in designating all these tumors. Such a term might well be "urotheliomata." A urothelioma would be defined then as a malignant urinary tract epithelial tumor probably arising from aberrant cell collections in the submucosa, and manifesting, in ad-

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A TUNNEL TECHNIQUE OF URETERO-INTESTINAL ANASTOMOSIS: AN EXPERIMENTAL STUDY

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The purpose of this study was to simplify the operative technique of implantation of the ureters into the rectosigmoid, with the hope of lessening the primary morbidity and mortality of this procedure.

To achieve this aim, the surgical principles of tunneling the rectosigmoid wall by the method of the submucous valve was combined, with some modifications.

The method was tried successfully with 4 dogs, although it is a common experience that it is more difficult to obtain good functional results in the laboratory, with dogs, than in the clinic.

The musculature of the dog's colon is composed of uniformly thick, longitudinal muscle fibres and there are no taenia or longitudinal muscle bands of great thickness in it, as in man's colon. From the underlying submucosa, in the dog's colon, the muscle layer is separated only with difficulty. This submucosa is practically inseparable from its mucosa and it is thin, but extremely tough and carries the blood vessels.

The ureter of the dog is very thin, but has a well defined sheath, similar to the human ureter, which in its terminal 2–3 cm. is very dense and fibrous in structure. This sheath should be used in an implantation to protect the ureter proper from undue traumatism. We can not expect an unimpaired physiologic function from a ureter which has been even slightly traumatized.

Technically the anastomosis of the ureter with the rectosigmoid, in dogs, is not so easy as it is in humans. It is necessary, for a successful union, that the intestine and ureter should not be traumatized very much. To achieve this aim, the following principles were set:

1) The ureter should be handled gently; trauma should be at a minimum, avoiding any angulation, torsion, tension, or compression. To avoid any *periureteric scars, the ureter should be exposed only as little as possible and there* should be used on it very few fine sutures, or none at all.

With these we try to reduce disturbances in transmission of the peristaltic wave of the ureter.

2) The new ureteral ostium should be large. Therefore it is split to avoid any undue contraction. This contraction may be due to the infection of the ureteral mucosa, producing a granuloma involving the whole new orifice, if it is not adequately large or, if there should occur an exudate in the wall of the bowel around the implanted ureter. The organization and subsequent periureteral fibrosis of this exudate with its edema, should only partially occlude the new orifice, not obstructing entirely the passage of the urine.

The split end of the new ureteral orifice should be brought against the wall of the bowel, thereby protecting the ureter against any retrograde direct infection, when the fecal material is forced into it and only touches it at a minimum.

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[1] Read before the Detroit Branch, American Urological Association, Windsor, Ontario, Canada, May 21, 1947.

3) To avoid any breakdown of the union with a eventual leakage, the blood supply of the intestinal wall should be disturbed no more than absolutely necessary.

4) It seems that those ureters do better that are placed for a short distance in the submucous connective tissue of the intestinal wall, but the distance should be sufficient to enable the ureter to be compressed by the intestinal pressure during bowel movement.

5) The operative technique should be simple and aseptic.

6) The immediate and late result of the operation should be consistently satisfactory.

Sir Harold Stiles introduced in 1907 an "external tunneling" method, when he buried the ureter in the wall of the sigmoid for a distance, in the manner of Witzel's oblique gastrostomy.

The principle of "internal tunneling" of the intestinal wall in ureterosigmoid anastomosis was first tried by Carl Beck, who tried to dangle the free portion of the ureter into the lumen of the bowel with the idea of preventing any infection or cicatrix formation of the ureteral orifice.

G. Marion in his textbook describes a method of tunneling the intestinal wall between two separate incisions, and Legueu and Papin modified this method.

Walker-Taylor with his "aseptic irreversible tunneling" employs the submucous principle with an aseptic technique, using a long needle attached to the ureter and guiding it through a tunnel, puncturing the intestinal mucosa into a previously passed rectal tube.

Thomas J. Kirwin describes a partially tunneling method, wherein he tries to create, with a catheter, an artificial tube or canal in the intestinal submucosa, between the cut end of the ureter and fecal canal. This method is not a tunneling one.

The technique which was used on 4 dogs, was the following:

The preoperative care consisted of a liquid diet for 3 days and sulfasuxidine, gm. 4 for the first day, gm. 2 for the second and third day. On the morning of the operation sulfasuxidine gm. 2 was given with water.

For perfect anesthesia intravenous nembutal solution was given gr. 1 in 1 cc per 5 pounds of body weight.

After proper preparation the skin was incised longitudinally for about 20 cm. to the right of the umbilicus.

This incision was deepened through the fascia, muscles and peritoneum.

The right ureter was lifted with an aneurysm needle.

With a small artery forceps, the right ureter was clamped as near to the bladder as possible.

The ureter was held up with this forceps and a double threaded fine silk suture was placed with a fine needle close to this forceps, on the proximal segment of the posterior surface of the ureter.

This silk suture was then tied.

A second suture but slightly distant from the first one was placed and tied. These sutures were used for slight traction.

The ureter was cut proximal to the forceps obliquely; the distant end was tied and allowed to drop back.

The proximal end of the ureter was held up by these traction sutures and was split for a distance of 1 cm. on its anterior rim, opposite these sutures (fig. 1, *a*, *b*).

The split ureter was held up with one suture, while one thread of the other suture was pushed with a fine needle into the lumen of the ureter at one corner of it. This thread was pushed from the lumen out again, through its wall and locked. (fig. 1, *c*).

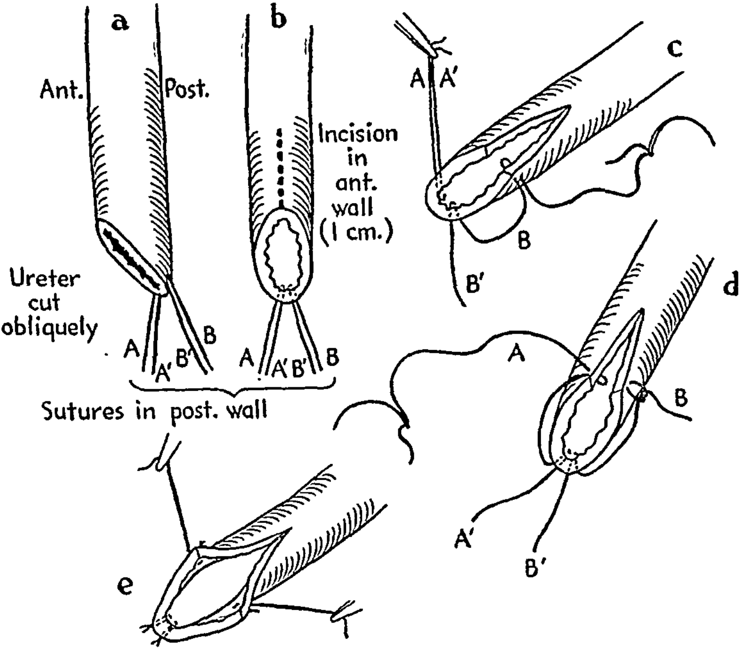

FIG. 1

The same movements were repeated with one thread of the second suture, on the other corner of the ureter. (fig. 1, *d*).

The remaining, middle threads of the sutures, were cut off.

The corners of the split ureter were held apart (fig. 1, *e*).

The split right ureter was placed on the anterior aspect of the rectosigmoid for measurement to avoid any subsequent tension.

A transverse stab wound is made with a sharp pointed knife through the serosa, slightly on the right side of the anterior wall of the rectosigmoid, but 1 cm. higher than the end of the ureter. This cut minimizes the damage to the blood supply of the intestine, as the blood supply surrounds the intestine transversely (fig. 2,*a*).

Place the wrapped end of the ureter to the side.

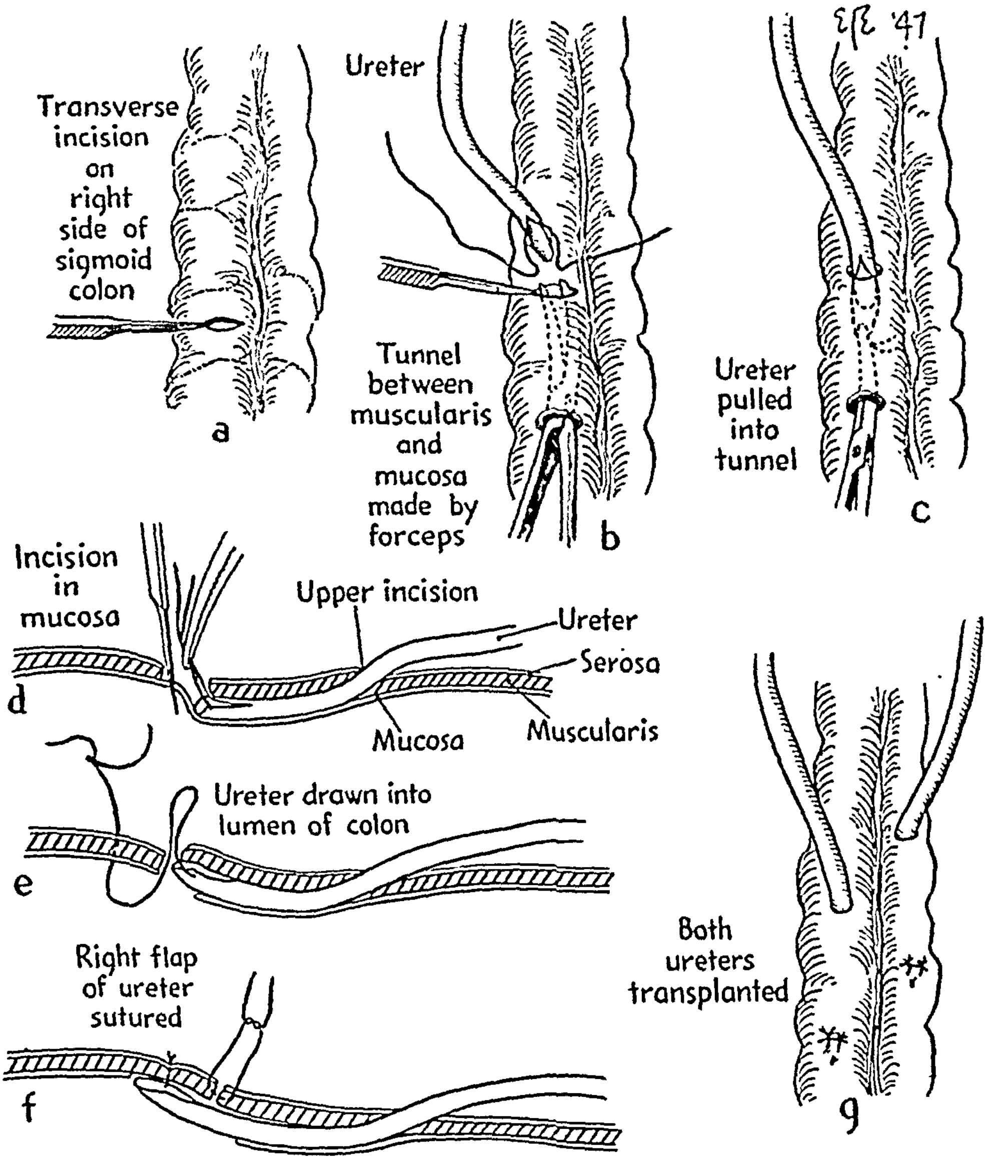
Transverse incision on right side of sigmoid colon
a
Ureter
Tunnel between muscularis and mucosa made by forceps
b
Ureter pulled into tunnel
c
Incision in mucosa
Upper incision
Ureter
Serosa
d
Mucosa
Muscularis
Ureter drawn into lumen of colon
e
Right flap of ureter sutured
f
Both ureters transplanted
g

FIG. 2

Through this transverse stab wound the muscularis of the bowel is pierced with a fine curved forceps. While separating the blades of the forceps, the mucosa is bulging up between them.

Pushing upwards and alternately opening and closing its handle between the muscularis and mucosa of the bowel for about 3 cm. this curved forceps provides a wide bed for the ureter, thereby preventing any subsequent constriction of the implanted ureter.

After tunneling for about 3 cm. depress the handle of this forceps and incise the serosa transversely between its blades (fig. 2, *b*).

Push tip of forceps through this incised serosal opening.

The ureter is grasped with this forceps by its two traction sutures, without needles, and pulled into the musculo-mucosal tunnel until its orifice appears at the lower end (fig. 2, *c*).

At this lower incision, the bulging mucosa of the bowel is pierced obliquely downwards with a fine sharp knife (fig. 2, *d*).

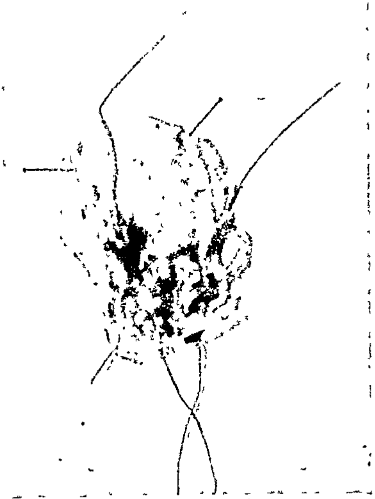

FIG. 3

Through this opening mercurophen solution (1/1000) was injected and sulfasuxidine powder placed into the lumen of the intestine.

Each corner suture of the ureter was threaded on a curved intestinal needle and pushed through this mucosal opening into the lumen of the intestine, for about 1 cm. beyond it, through all coats of its wall and out again (fig. 2, *e*).

After tying these sutures together the ureter is drawn into the lumen of the intestine and held firmly in its place, making a slight upward curve with its slit orifice (fig. 2, *f*).

These transfixion sutures may cause a little dimple on the surface of the serosa, where a Lembert suture may be used.

The transverse incision is approximated with one or two fine sutures.

The identical steps are taken on the left side, only the initial transverse incision on the anterior wall of the rectosigmoid should be at a slightly higher level than the right one (fig. 2,*g*).

This uniform technique was used on 4 dogs averaging 30-32 pounds. The result of the ureterorectosigmoidal anastomosis was excellent with each one, proven by postmortem examinations. Unfortunately the first dog died on the sixth day of pelvic cellulitis, caused by the cystectomy, which was performed at the same time as the anastomosis. The third dog died on the ninth day from pneumonia. The second dog was sacrificed on the sixth day and used as a control for the first dog. The fourth dog was sacrificed after 75 days (fig. 3).

COMMENT

The following points of the technique are stressed:

As the blood supply surrounds the rectosigmoid transversely, a transverse incision causes less damage than a longitudinal one. (Davalos.)

The longitudinal intestinal tunnel does not sharply sever blood vessels, therefore the intestinal wall is not weakened as much as in the other techniques, with their circulatory disturbances caused through the customary construction of the ureteral bed.

With tunneling, the layers of the intestinal wall are not approximated too tightly over the ureter and thereby its circulatory disturbances, through pressure, are lessened.

As the transfixion sutures are placed only after measurements, they eliminate any tension or kinks of the ureter, which thereby holds trauma to a minimum. These sutures also insure that the ureter is not pulled out from the rectum.

The enlarged ureteral orifice insures an early resumption of the normal peristalsis and function of the ureter; consequently the renal function does not suffer much interruption.

As the lumen of the bowel, the infected territory, is only exposed slightly, the operative procedure is as aseptic as possible.

This simplified operative procedure does not demand a higher technical skill or knowledge. It points toward a more radical thinking in this line, whenever this operation should be done. It points a way to a more satisfactory result in the treatment of the so rapidly fatal bladder cancers, or the intolerable sufferings from a tuberculous bladder patient or the incontinence of an ectopic bladder.

As only the immediate relief and the lessening of the primary mortality and morbidity were considered in devising this operative procedure, we still accept, at present, the same remote results and delayed complications, which follow the other operative techniques, such as urine absorption, pyelitis, dilatation of the ureters, hydronephrosis, renal infections, and impairment of renal function.

SUMMARY

A 1-stage intraperitoneal technique in dogs is described as a bilateral uretero-rectosigmoidostomy, with the selection of the site of the anastomosis.

With a tunnel technique, a valve control is established between the ureter and rectosigmoid.

During this simple operative procedure the intestinal and ureteral trauma is minimized.

Surgical asepsis is maintained.

My appreciation is expressed to Dr. Charles G. Johnston for his interest, and to Dr. Murray S. Bergman for his assistance.

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barrassment. For this reason they are usually social outcasts and live an isolated life. The bladder may become excruciatingly tender and areas of phosphatic encrustation frequently occur. These patients have a peculiar waddle or duck-like gait—more of a shuffle than a normal walk. They seldom sit in an upright posture but slump down in the chair and rest more upon the lumbar area than the buttocks. These peculiarities are caused by the marked separation of the transverse rami of the symphysis pubis and the outward rotation of the femora. As a result of the malformation of the recti muscles and fascia, the majority have inguinal or femoral herniae. On account of their grotesque sexual appearance and repulsive urinary odor, most of these patients are forced to lead an asexual life. While coitus is entirely impossible in the male, due to epispadias and the lack of a urethra, the act is not impossible in the female. While it is agreed that coitus must be a most distasteful act to the partner, nevertheless Winslow describes an exstrophy in a female who had had 4 children. A résumé of 145 cases seen in 20 years at the Mayo Clinic revealed that 35 of these were females, and of the 5 of this group who underwent uretero-intestinal anastomosis, 4 later gave birth to children.

It is rather interesting that in a group of persons who have led such isolated lives under such trying circumstances more psychoses have not developed. The only peculiarities noticed are marked timidity and an inferiority complex engendered by social isolation.

PROGNOSIS

According to Newdorfer and Marion, nine-tenths of these patients die before reaching the seventh year. Mayo and Hendricks claim that 65 per cent will not live long enough to vote.

The bladder, being wide open, is a fertile field for bacterial growth, and the usual pathological change is pyelonephritis or pyonephrosis which results in death.

DIAGNOSIS

Because of the prominent physical defect, a diagnosis can readily be made without the aid of laboratory tests or instrumentation.

TREATMENT

It is most essential that the patient have the proper care preoperatively if the surgeon wishes a smooth postoperative course and the survival of his patient. With present-day chemotherapy, it is unusual to see a stormy postoperative course from intestinal contamination and renal sepsis, such as were so frequently seen years ago. I do not think I exaggerate in saying that the patient has today a 75 per cent better chance than he would have had before the sulfa drugs, penicillin, and streptomycin were brought into the realm of surgery.

It is advisable to cleanse and sterilize the lower bowel as well as possible befroe doing any surgery. This is accomplished by placing the patient on a light diet for 5 to 7 days preceding the operation and administering 0.25 gm. per kilogram of body weight of sulfasuxidine daily. This daily dose is divided into 6 portions, 1 every 4 hours. Sulfasuxidine is the choice of the sulfa drugs because it is of low toxicity and sterilizes to a great degree the bowel as well as the kidney. Copious water drinking is encouraged, and 2 days prior to surgery the patient is placed on a liquid diet. Soap suds enemas are given morning and evening, except the morning of the operation. This last enema is avoided because often, if the edema is not completely expelled, the patient arrives in the operating room with a filled bowel.

Some surgeons, in order to quiet peristalsis, give a dram of paregoric every 4 hours for 3 doses before surgery.

Palliative: Various ingenious devices, as well as various extraperitoneal surgical approaches, have been attempted from time to time to correct this unfortunate malformation. Some patients, especially those who have survived the first decade, are poor surgical risks owing to the hydroureters and pyelonephritis that already exist. It is in these cases that such palliative measures as cups or retainers which catch the urine should be applied. This will result in dry clothing and the loss of the obnoxious urinous stench which is so characteristic of these patients. These funnels, cups, or containers are made of such products as rubber, aluminum, silver, and chromium, and the majority empty into a rubber bag which is strapped to the thigh or leg. While these devices are aids, in general they are wholly unsatisfactory and inefficient for they cannot be worn at night, and after much wear cause ulceration and excoriations of the abdomen due to the friction from movement and clothing. Such skin lesions must be treated with ointments and infra-red lamps to control them. The majority of these victims are so uncomfortable most of the time that they present themselves willingly for open surgery even after the hazards of such a major procedure have been enumerated.

Extraperitoneal surgery: This includes various methods of plastic work upon the bladder and the urethra with the objective of diverting the urinary stream and keeping the patient dry. While brilliant cosmetic results were obtained by some operators, the pitfall to this approach was the inability to re-establish sphincteric control. Nearly all of these plastic operations have been abandoned today. Young, however, does cite 1 case of a female upon whom he had done several plastics, using his usual ingenious methods, which ended up with a normal, functioning bladder. Other operative procedures, including transplantation of the ureters to the loin and groin, even excising the vesical mass surrounding the ureters and transplanting this, have all proved to be unsatisfactory as regards mortality and diversion of the urinary stream.

The best results today are obtained by radical surgery, which involves complete removal of the bladder and diversion of the urinary stream into the rectum. The pioneers in this field had much difficulty because they failed to provide for valve action at the site of transplantation into the bowel. The rates of morbidity and mortality were extremely high, due to sepsis, shock, and ascending pyelonephritis.

With modern refinements in technique and with the advent of such therapeutic agents as the sulfa group, penicillin, and streptomycin, the results have been much more gratifying and the morbidity and mortality rates amazingly reduced.

The opportune time for surgery has been the subject of much controversy. While it is now generally conceded that one should no longer wait until the tenth year, it is still questionable whether it is advisable to attempt this difficult operation in early infancy. The author is in accord that in malignant bladders the transplants should be done early and not as a last resort after all other methods have failed and the metastasis has involved the vesical end of the ureters, causing stenosis and definite renal damage. Higgins advises transplantation before the first year, preferably before the sixth month, because of the increased incidence of pyelonephritis as the child grows older and the less virulent organism of the infant bowel. While these points are well put, there are several hazards involved in infant transplants, namely: a) the difficulty of identifying and working with these small and delicate structures; and b) the questionable rectal sphincter control in infants of this age.

It is true that a great number of patients with exstrophy undergo ureteral dilatation and pyelonephritis, but this does not occur in all cases. In the author's case, the ureters and renal pelves were normal in a 37 year old male. Unquestionably, in older patients the ureters are more easily handled, the lumen is larger, and the gut less delicate to handle. It is possible that with the administration of our newer drugs these infants may be tided over until later years when the anatomical structures are more discernible and easier to repair.

Although there are 60 to 70 different techniques for ureteral transplantation into the bowel, the ideal method is probably still to be found. Most operations are modifications of the Coffey technique as described by him in 1911, the techniques most popular today being as follows:

Technique I: The ureters are transplanted individually, the right one first. The ureter is drawn into the interlamellar space above the intestinal mucosa and the slit end is drawn through an ostium made through the mucosa at the caudal end of the incision and thus anchored inside the intestine.

Technique II: This operation is similar to the above except that a tube, or catheter, is placed in the ureter and fastened with sutures. The catheter is then passed through the opening made in the gut and drawn into the intestinal lumen. The urine drains through the ureter and catheter into a receptacle outside the body. The intra-intestinal ureter is subjected to intralamellar pressure at the point of transplantation only after the intra-intestinal end of the ureter sloughs, which is 8 to 10 days after the operation.

Technique III: In this operation, the ureter is brought into the intralamellar space outside the mucosa by an anchor stitch of chromic catgut which fastens the ureter to the caudal end of an incomplete intestinal incision. The anastomosis is finally made by a fine linen suture which is tightly tied so as to transfix both ureter and intestinal mucosa. The anastomosis is complete within 3 to 4 days after the operation.

Higgins' technique is a modification of the Coffey III technique. He suggests placing the intact ureter upon the mucosal layer in a 6½ cm. trough. At 1 cm.

from the caudal end of the trough, a silk suture is passed through the wall of the ureter and through the intestinal mucosa to act as a mattress suture The suture is tightly tied and muscular serosa layers of gut pulled over the ureter, which lies in the trough made for it Later a fistula becomes established which should prevent ascending infection from the bowel and in no way interfere with the passage of urine from the kidney to the bowel

Jewett's method differs but slightly from the above, except that he uses an ingenious electrode, which he has perfected, to complete the ostium into the ureter and the gut He does bilateral transplants, leaving each ureter intact in its intestinal trough for 3 weeks prior to establishing the uretero intestinal ostia with the instrument he has devised for this procedure

Other methods of ureteral anastomosis have been devised by Hutchins, Hinman, Nesbit, Poth, White, Wharton, and many others

Every surgeon, in his respective operation, seeks to achieve two results which spell success if accomplished and defeat if not a) free urinary drainage from the kidney into the bowel, and b) avoidance of fecal contamination ascending up the ureter into the kidney

CASE REPORT

This case is rather unique in that this patient had attained the age of 37 without seeking any medical or surgical advice He was raised in the Ozark hills, and his only form of medication was repeated changes of abdominal pads to absorb the urine which extravasated continuously over his abdomen While he had remissions of slight nausea and fever, his health, considering his congenital defect, was quite good He finally sought surgical aid because, due to his ever present urinous odor and the necessity of frequent pad changes, he was a social outcast His bladder wall also became so ulcerated at times from being constantly urine-soaked and exposed that he was periodically forced to bed rest Although ostracized from society, he was taught by his sister, a school teacher, and has passed his examinations as an electrician

This 37 year old unmarried man, when he presented himself, had the typical exstrophy gait and squat described above

The head and neck were found negative The chest was well developed, with the apex beat in the fifth intercostal space No murmurs nor arrhythmia were heard The chest was clear with an occasional light wheeze around the bronchial tree

The upper abdomen was normal in appearance, but suprapubically a reddened, ulcerated area the size of the palm of an adult hand was seen The anterior abdominal wall was entirely lacking and the bladder everted upon the abdominal surface The ureteral orifices were plainly visible and spurts of urine could be seen as it was excreted from time to time The recti muscles and their attachments were lacking suprapubically as was also the symphysis pubis, with a 4 inch separation of the pubic bones (fig 1)

The penis was normal in length with a rudimentary urethra at the peno abdominal juncture A complete epispadias existed with a flattened anterior surface of the shaft of the penis. The testicles were normal in size and position. A double hernia was noted. The epididymes and vasa felt normal. The prostate was quite flat and small in circumference and soft. The patient claimed he was capable of erections and ejaculations (fig. 2).

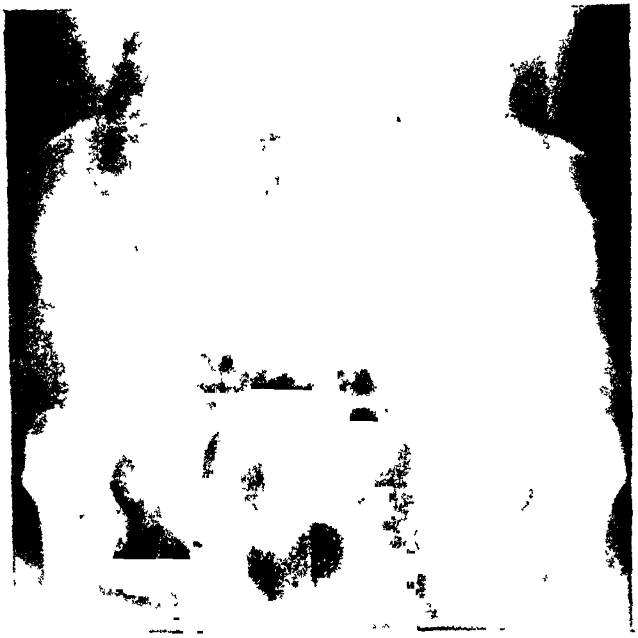

FIG. 1. Bony architecture of exstrophic patient, illustrating marked separation of transverse rami of pubis and outward rotation of femora.

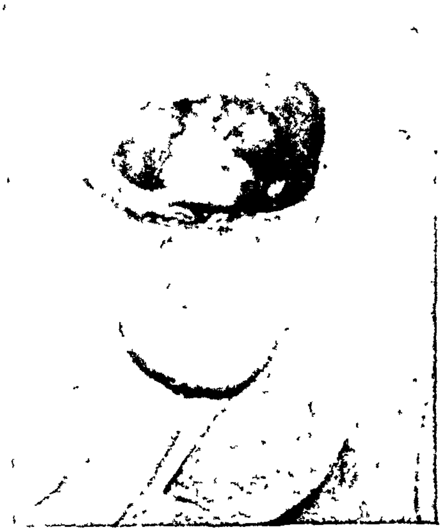

FIG. 2. Preoperative exstrophy of bladder, showing absence of anterior abdominal wall, ulcerated bladder mucosa, and complete epispadias with rudimentary urethra.

The lower extremities were extremely well developed, the thighs and calves displaying well-formed muscles.

On May 16, 1946, intravenous pyelograms were done in order to interpret the condition of the upper urinary tract prior to surgery. The pyelograms at this time showed well-distended kidney pelves with normal ureters. There was little or no evidence of old infection nor hydroureters (fig. 3).

Preoperative treatment consisting of light diet and the administration of 45 gr. of sulfasuxadine every 4 hours was started This was continued for 4 days and a cleansing enema given the morning and evening of the fifth day with liquid diet only the fifth day.

On May 22, 1946 bilateral uretero-intestinal anastomosis was performed. A midline abdominal incision was made, extending upward from the symphysis pubis for about 6 inches. There was practically no recti muscle nor fascia. The fascia that was found was adherent to the peritoneum. The peritoneum was opened and the intestines were pushed to one side, allowing the ureters, which had previously been catheterized, to be easily discerned along the lateral peritoneal folds on each side An incision was made in the right side and the right ureter dissected free for about 4 inches. It was then tied low and bisected. The end of the ureter which was to be anastomosed was slit on each side (fish mouth) and an 0 chromic suture placed in each peak of the fish mouth. The area chosen on the sigmoid was trenched for about 4 inches down to the top of the submucosal layer and the ureter placed in this area. An ostium was made at the lower end of this tunnel and the ureter drawn through the ostium into the gut by means of the sutures placed in each peak of the fish-mouthed ureter. The 2 sutures were then tied together an inch below the ostium upon the serosa of the gut. In this manner the ureter was held bilaterally in the gut by a suture on each side. Three sutures of 00 chromic gut were placed through the serosa and part of the ureter in order to keep the ureter intact. A running suture of 00 chromic was placed over the tunnel, closing the serosa over the entire area.

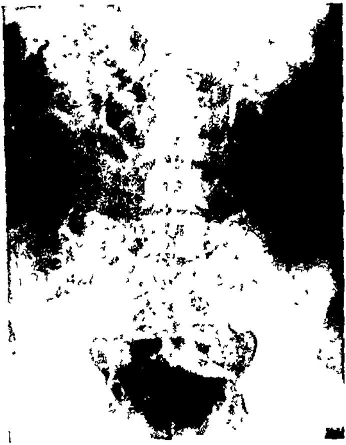

FIG 3. Preoperative intravenous pyelograms, showing quite normal pelves and ureters after open bladder had been exposed to infection for 37 years Nonprotein nitrogen 21.

The parietal peritoneum was then sewed over the gut to the gut wall in order to extraperitonealize the transplant. The sigmoid, by means of 2 or 3 sutures, was pulled up to the parietal peritoneum after the transplantation in order to immobilize the gut.

A similar procedure was done on the left side. Two drains were then placed, one at the base of the right transplant, and the other at the base of the left transplant. After lavaging the wound with saline solution, the peritoneum was closed with No. 2-20D chromic with interrupted sutures. The fascia was closed with No. 2-20D chromic with a running suture.

Three retention sutures were placed in the abdomen and the skin closed with black silk.

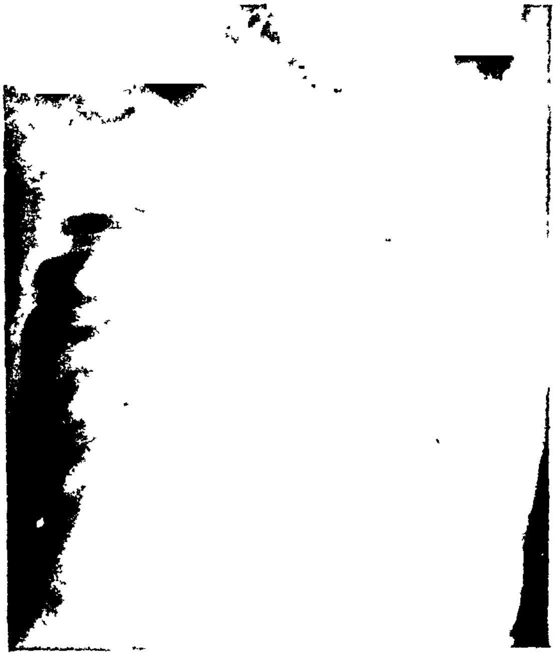

FIG. 4. Demonstrates infiltration of entire left lung and lower two-thirds of right lung after administration of parenamine.

The postoperative course was quite stormy the first few days, with the patient suffering from much abdominal distension and discomfort. A rectal tube, which had been inserted in the operating room, was left intact and a Miller-Abbott tube passed into his stomach. The third postoperative day he was given 100 cc of parenamine in 1000 cc of 5 per cent glucose intravenously. He became cyanotic, began to have wheezing and labored respirations, and his chest appeared to be filling up very rapidly. A portable x-ray was taken which showed an infiltration throughout his entire left lung and a haziness throughout the lower two-thirds of the right lung. The diagnosis was: "Pneumothorax and pneumonic infiltration." (fig. 4)

The cyanosis, labored respirations, and abdominal distension continued for 4 days, after which it was decided that he had protein sensitization and that the parenamine was the offender.

Aminophylline ($3\frac{3}{4}$ gr.) and ascorbic acid caused an almost miraculous change for the better, and in 24 hours all his discomfort had disappeared. During his entire postoperative course, he was kept on penicillin and sulfasuxadine. The rectal tube was removed on the tenth postoperative day.

On July 9, 1946, about 6 weeks after the bilateral transplants, a total cystectomy was performed. The exposed bladder mucosa and all bleeding points were controlled by catgut ties and sutures, the lateral flaps were then undermined and released toward the scrotum and laterally. All tissues were handled carefully and every effort made not to devitalize tissues with crushing forceps. The abdominal fascia was closed over the sutured bladder muscularis and fascia, thus making a strong wall.

The skin was then brought together in the midline and sutured above and below. A small Penrose drain was placed in each inferior angle and a sterile dressing applied. The patient had a rather uneventful convalescence. His temperature remained near normal until the fifth postoperative month.

He then returned with severe pains in the left lumbar area and began showing a spiked temperature. Intravenous pyelograms showed diminished left renal function and definite signs of hydronephrosis (fig. 5, *A*). Several unsuccessful attempts were made to do a retrograde catheterization through the proctoscope (fig. 5, *B*).

It was finally decided to do a left ureteral exploration. McBurney's incision was made over the left anterior iliac spine and an attempt was made to find the ureter extraperitoneally, but it was located intraperitoneally. The ureter was opened a few centimeters from its ostium in the gut and attempts were made to establish its patency into the gut by passage of ureteral catheters, bougies, and probes. All of these attempts were unsuccessful, and it was impossible to enter the gut in this manner. The Jewett cautery electrode was introduced into the lumen of the ureter and an attempt made to produce a new ostium by applying the fulgurating current. This also failed, and so the cutting current was applied which produced an ostium but also produced excessive hemorrhage from the incision of a good-sized vessel in the gut. This was ligated with difficulty. A few inches of sigmoid was extraperitonealized and the original incision in the ureter was sewed to the sigmoid colon by effecting a side-to-side anastomosis with catgut. The initial incision over McBurney's was closed in layers with interrupted No. 1-20D chromic after sulfanilamide powder was sprinkled in the wound. A rubber dam drain was brought out at the lower end of the wound and the skin closed with running silk.

The patient tolerated the operation well and was returned to his room in good condition. He had but slight reaction to the procedure on the third postoperative day, and thereafter for 5 days he had complete relief from left renal pain and backache. Three weeks after this operation, he again ran a spiking temperature and a steeple-chase curve. One month after this operation another intravenous pyelogram (fig. 5, *C*) was run which now showed bilateral hydronephrosis with bilateral hydroureters.

The patient has been able, from experience, to estimate by the amount of

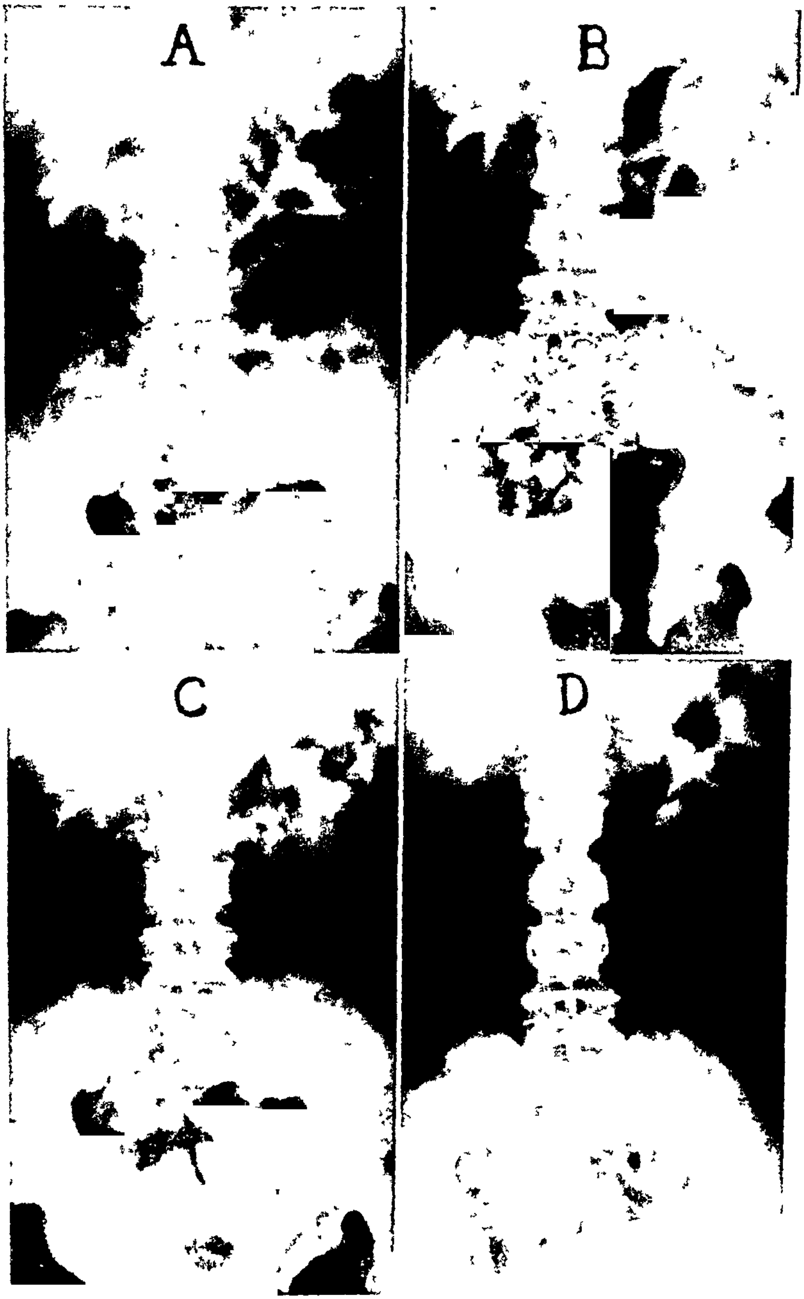

FIG. 5 *A*, Intravenous pyelogram, made 4 months after transplants, shows some delayed emptying on both sides with evidence of hydronephrosis on left. Nonprotein nitrogen 24. *B*, Intravenous pyelogram, made 6 months after operation, showing increase of hydronephrosis on left with fairly normal pelvis on right. Nonprotein nitrogen 23. *C*, Intravenous pyelogram, 8 months after original transplant and 1 month after side-to-side anastomosis on left ureter. No increase in left hydronephrosis. *D*, Left pyelogram when patient was discharged from hospital. Definite reduction in size of hydronephrosis on left side, demonstrating good function after side-to-side anastomosis

urine released per rectum whether or not there is urinary obstruction. While he is ambulatory and capable of light work, he is definitely not a normal individual, owing to his periodic attacks which temporarily incapacitate him. His last appearance was quite gratifying in that after a 6 week release from the hospital he had gained 12 pounds and looked exceptionally well (fig. 5, *D*). His kidney pains and febrile attacks show a definite decrease in frequency since his discharge, the patient stating that he now feels normal in all respects and has had but one attack of pyelitis in 5 weeks. While it is true that he had pyelitis attacks previous to this surgery, it is also evident that he occasionally has them now, although we have accomplished *one* thing—relief from urinary extravasation and urinary stench, for which he is very grateful (fig. 6). It is possible that his sphincteric control is becoming perfected with time and that he eventually will lead a life of renal normalcy.

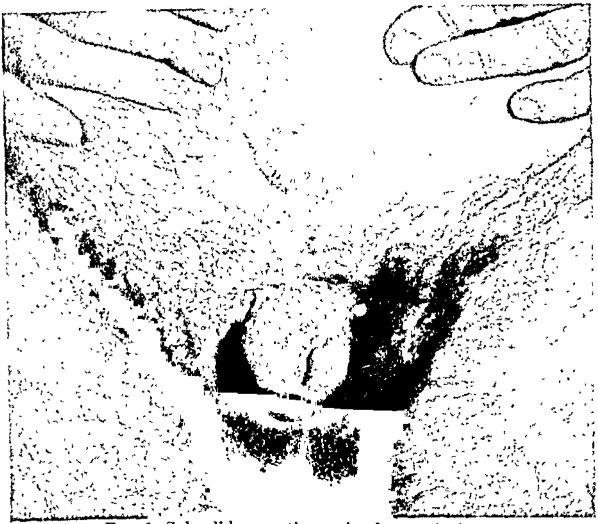

Fig. 6. Splendid cosmetic result after cystectomy

CONCLUSIONS

That some cases of exstrophy can reach the third or fourth decade with but mild attacks of pyelitis and evidence but slight renal destruction.

That with the advent of new therapy better results can be accomplished with more radical surgery with fewer and milder reactions.

That a side-to-side anastomosis apparently permits as favorable drainage as is accomplished in other techniques.

That either ascending infection or urinary obstruction individually or the two combined are still the contending factors against satisfactory end results.

That the ideal method of uretero-intestinal transplantation is still to be perfected.

The author is indebted and grateful to Dr. Charles Sherwin of the Barnard

Skin and Cancer Hospital for his kind assistance and helpful suggestions in securing the splendid cosmetic results in the plastic surgery in this case.

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CARCINOMA AND SARCOMA OF BLADDER REPORT OF UNUSUAL SIMULTANEOUS OCCURRENCE OF BOTH TUMORS

A MACKLES S IMMERGUT, D M GRAYZEL AND Z R COTTLER

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Multiple tumors, especially malignancies, occur very infrequently in one organ Usually, as in the intestinal tract, they are of one type and most commonly of epithelial origin The occurrence of two distinct and entirely dissimilar neoplasms is most uncommon and, especially so, is the joint presence of carcinoma and sarcoma in one organ An exhaustive search through the literature has failed to disclose a single case resembling the one we are reporting

In 1943, Crane and Tremblay collected 151 cases of sarcoma of the urinary bladder, their group included 7 cases of leiomyosarcoma Recently, Lev and Bell presented a case of leiomyosarcoma of the bladder and summarized the 14 cases collected by Kretschmer and Doerling as well as the 7 cases of Crane and Tremblay The present case is the twenty-third reported instance of leiomyosarcoma of the urinary bladder

CASE REPORT

H N, Jewish Hospital case No 399511, a 52 year old white male grocer, consulted one of us (S I) on January 10, 1947 because of frequency and dysuria of 2½ years' duration and hematuria for the past 1½ years He had been perfectly well until the onset of these symptoms, when he noted burning on urination and nocturia, at least once a night On admission he voided every 2 hours, day and night, with severe pain The hematuria had been almost constant Oral medication had been prescribed by a general practitioner but no relief of symptoms had been obtained A urological survey had never been suggested The urine was grossly bloody Rectal examination disclosed the presence of a firm, non-tender mass above and distinct from the right lobe of the prostate The gland itself was not enlarged, hard or nodular An excretory urogram revealed no function of the right kidney, even after 1 hour The left upper urinary tract showed the presence of the dye and was moderately dilated from the calyceal cups down to the ureterovesical function There was a crescentic filling defect at the base of the bladder, more marked on the right (fig 1)

The patient was admitted to our service at the Jewish Hospital on January 14, 1947 Physical examination, except for the rectal, showed no abnormalities The blood pressure, pulse and temperature were normal

Laboratory data Hemoglobin 88 per cent, erythrocytes 4,070,000, leucocytes 14,650, polymorphonuclears 73 per cent, bands 2 per cent, lymphocytes 22 per cent, monocytes 3 per cent Urine Alkaline, albumin 3 plus, sugar negative, microscopically, 10 to 12 white blood cells and 40 to 50 red blood cells Phenolsulphonphthalein test. 29 I per cent in 2 hours Urine culture B pyocyaneus Blood chemistry Urea nitrogen 32 8 mg per cent, sugar 108 mg per cent; uric acid 6.0 mg. per cent; carbon dioxide combining power 56.9 volumes per cent. The Kline test was negative.

Radiographic studies of the chest and spine were negative for metastases.

Cystoscopy, under spinal anaesthesia, revealed almost the entire bladder, except for a small portion of the dome, to be covered with thick, friable, papillary masses which bled freely on manipulation. Neither ureteral orifice could be visualized, and the neoplastic masses extended right up to the vesical neck. Several biopsy specimens were removed and reported as papillary carcinoma.

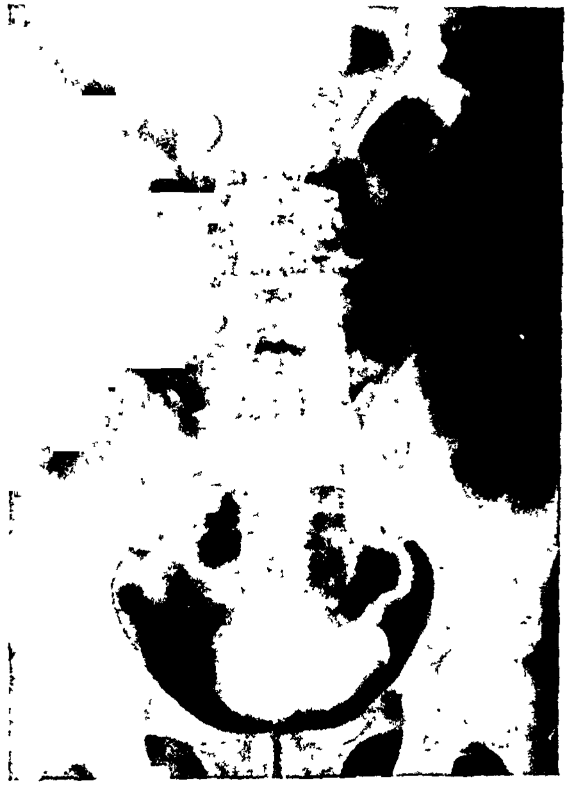

FIG. 1. 75 minute excretory urogram. Practically no function on right side; marked hydroureter and hydronephrosis on the left. Right side of bladder is rigid and limited by tumor.

A cysto-aerogram also showed the presence of the crescentic filling defect and numerous negative shadows suggestive of neoplasm.

A Foley catheter was placed in the bladder and the patient prepared for operation. Inasmuch as there was evident damage to the left upper urinary tract, it was felt that an effort should be made to salvage what was possible of the function of the right kidney. Accordingly, we planned and undertook a 3-stage procedure in the following order: 1) a right cutaneous ureteroneostomy, 2) a left cutaneous ureteroneostomy, and 3) a total cystectomy. Intestinal transplantation of the ureters was considered inadvisable because of their dilatation.

On January 24, with the patient under nitrous oxide-ether-oxygen anesthesia, the right ureter, dilated to 3 times the normal size, was approached through a right oblique, muscle splitting incision, extraperitoneally (S. I. and Z. R. C.). It was divided well below the level of the iliac vessels, and the proximal end intubated with a No. 16 F. latex urethral catheter. This was brought out through the wound so that 1 inch of the ureteral stump protruded beyond the skin surface. The point of emergence was approximately 1½ inches above and medial to the anterior superior iliac spine. The convalescence was uneventful. The output from the right kidney rose from 100 cc. to 800 cc. daily. The phenolsulphonphthalein test on January 30 showed the excretion from the right kidney to be 2.55 per cent in 2 hours, and from the left to be 21.55 per cent. The urea nitrogen fell to 22 1

On February 6, under cyclopropane anesthesia, a similar procedure was carried out on the left side. The left ureter was found to be dilated to a greater degree than was the right. The output from the left kidney averaged between 800 to 1250 cc. per 24 hours. The smooth convalescence was interrupted by an episode of acute left pyelonephritis, as evidenced by a chill, fever, left costovertebral tenderness and positive culture of the left kidney urine for *B. coli* and *B. pyocyaneus*, on the ninth postoperative day. Under treatment with streptomycin and sulfathiazole, he became afebrile after 6 days. It was decided to wait and prepare the patient with transfusions and infusions before undertaking the final stage of our planned procedure.

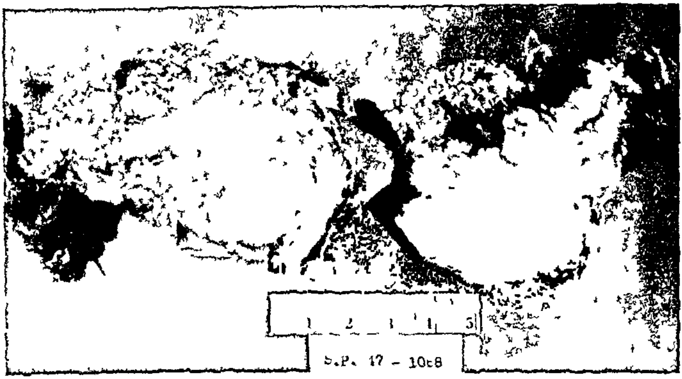

FIG. 2. Hemisected gross specimen. Note papillary carcinoma above and homogeneous sarcomatous mass below.

Thirty-nine days after the second ureterostomy, under spinal pontocaine anesthesia, total cystectomy was performed through a suprapubic midline incision. The bladder, ureteral stumps, seminal vesicles and prostate, except for a small distal portion, were removed in toto. It had been intended to open the peritoneum and explore the liver, posterior aspect of the bladder, and other organs, but in freeing the dome of the bladder, which was remarkably thin, and, in areas, devoid of musculature, it perforated and there was a tumor spill. This made us abandon the exploration. There was a very firm, hard mass in the region of the right ureteral orifice which corresponded to that felt rectally. Although adhesions were present in this area, a clean plane of cleavage was established and no difficulty encountered during the procedure. Drainage was established both suprapubically and perineally through a counter incision. Convalescence was remarkably uneventful.

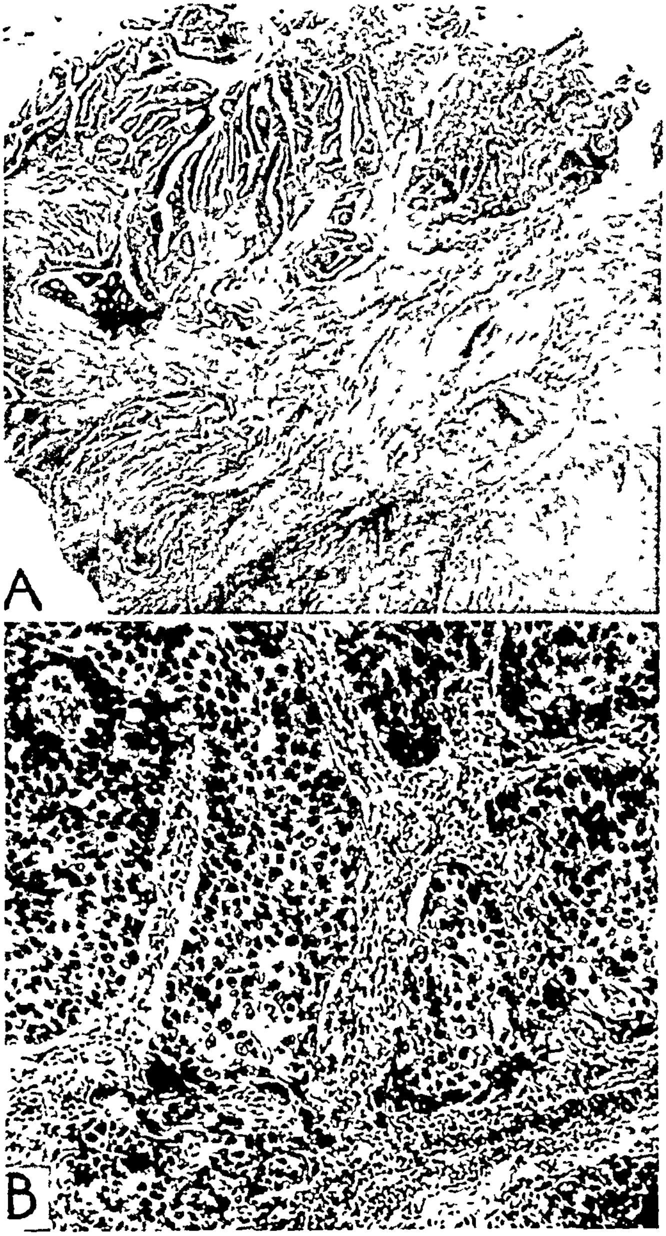

FIG. 3 *A*, Photomicrograph, showing papillary carcinoma above and leiomyosarcoma below *B*, Showing papillary carcinoma.

Pathological report (A. M. and D. M. G.): The gross specimen consisted of a previously opened urinary bladder with attached seminal vesicles, ureteral stumps and portion of the prostate The external surface was gray and red, and roughened by fibrous tags The mucosa was replaced by friable gray-orange papillary tissue The wall measured up to 1 5 cm in thickness except for an area at the base in which the wall was replaced by a firm mass, 5 by 4 by 4 cm, which merged indistinctly with the adjacent tissue On section, the cut surfaces were homogeneous, gray, and the central portion contained several irregular, soft, bright yellow, clearly outlined areas up to 1 cm in greatest dimension The seminal vesicles and prostate were not unusual See figure 2

Microscopic One preparation showed at one end a tumor composed of urothelial cells in nests or mounted on connective tissue stalks The cells varied in size and shape and in nuclear stains Mitotic figures were fairly numerous There were foci of necrosis and the tumor extended into the muscular coat In the deeper portion there was another tumor composed of spindle-shaped cells of varying size Here, too, the nuclei were hyperchromatic and many were in mitotic division The cells were in intertwining bands Occasional giant tumor cells were present Foci of necrosis were also present in this tumor In occasional areas both types of tumor were present Tumor cells were also seen within lymphatics Scattered within the tumor mass were fragments of the muscular wall Diagnosis Urinary bladder with papillary carcinoma and with leiomyosarcoma See figures 3 and 4

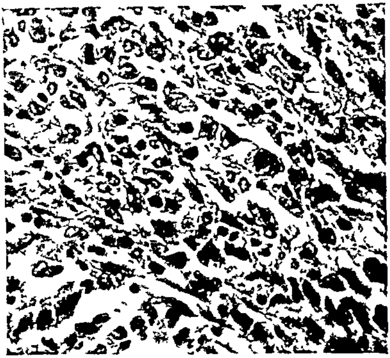

FIG 4 Showing leiomyosarcoma Note mitotic figures

At the present time, 6 months after operation, both ureterostomies are functioning well However, rectal examination reveals the presence of a small hard nodule on the right side and a radiograph of the chest reveals the presence of pulmonary metastases The suprapubic midline incision has healed except for the lower angle which intermittently discharges pus and blood Although both these neoplasms are considered radio resistant, a course of therapy has been started as a palliative measure He has gained weight and his hemoglobin is 100 per cent

SUMMARY

A case is presented which is unique in that both a papillary carcinoma and a leiomyosarcoma are present and existing independently of one another in the same urinary bladder. This is the twenty-third reported case of leiomysarcoma of the urinary bladder reported in the literature.

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CARCINOMA WITHIN A DIVERTICULUM OF THE BLADDER[1]

CARL K. PEARLMAN AND RAY M. BOBBITT

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Carcinoma in a diverticulum of the bladder is considered to be a rare lesion. In Lower's series of 157 cases of bladder diverticula, tumor was associated with diverticulum in 8 cases, in 2 of which the tumor was in the diverticulum. Goldstein and Abeshouse in 1943 were able to review only 94 cases of cancer confined to a diverticulum of the bladder. Muellner is of the opinion that this type of cancer is encountered considerably more often than the figures indicate. He ascribes this to the fact that most instances of carcinoma in a diverticulum simply are not reported. Undoubtedly, many are missed because the interior of a diverticulum is not visualized easily. In a discussion with some members of this society, after the presentation of his case, Muellner found that a few urologists present could account for well over a dozen such cases, none of which had been reported.

Bladder diverticula are treated conservatively as a rule, and removal of the obstruction at the vesical outlet is considered to be sufficient unless the diverticulum is non emptying or causes obstruction to the ureter. If the incidence of carcinoma in a diverticulum is much greater than believed heretofore, the pertinent question, as has been suggested by some investigators, is whether excision of most diverticula should be the treatment of choice. The following case is presented in order that future statistics may be improved by its inclusion.

CASE REPORT

A 76 year old man was admitted to the hospital on October 20, 1946 because of gross hematuria and passage of clots, of 10 days' duration. Except for pain while passing the clots, he had no other urinary symptoms. There was a loss of weight of 35 pounds in the past year. Prior to the onset of the present illness, he had no urinary symptoms.

On examination, he was found to be an elderly, thin, white man who exhibited the residuals of an old left hemiplegia, hypertension, and coronary arteriosclerosis with grade 2 heart disease. No abnormal masses were palpated on abdominal examination. Rectal examination revealed a small, firm, movable prostate. There was no induration of the bladder base or fixation of the bladder, on bimanual examination. On cystoscopy, a mass was seen which appeared to be a necrotic tumor with hemorrhage into it on the left side of the bladder. There was no prostatic enlargement or bladder neck contracture. Biopsy of the mass showed only old, partly organized blood clot. Therefore, cystoscopy was repeated and several ounces of old and fresh blood clot evacuated. The lesion previously described as a tumor consisted entirely of blood clot which was removed by frequent washings and suction. A diverticulum with an orifice approximately 1 cm. in diameter was then visualized near the left ureteral orifice (fig. 1).

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Within the diverticulum, the papillary processes of a tumor were seen. A piece of tissue, removed by cystoscopic biopsy forceps, was reported by the pathologist as papillary carcinoma. Both ureters were easily catheterized to the renal pelves. Urinary effluxes were clear. Retrograde pyelography was not attempted since intravenous pyelography had been obtained previously and showed

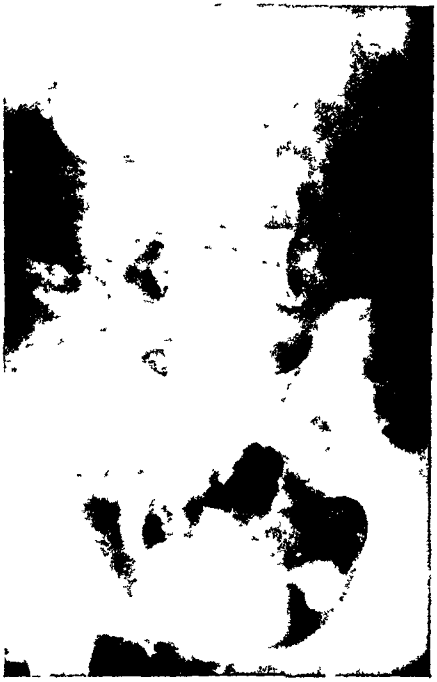

FIG. 1. Cystogram, showing diverticulum on left, also reflux into right ureter and renal pelvis.

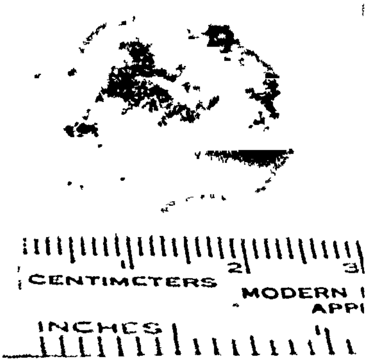

FIG. 2. Specimen removed at operation

poor renal function but no gross abnormalities. X-ray studies of the chest and bones showed no evidence of metastases. Because of poor renal function, as well as for the prevention of recurrent clot formation, drainage was instituted by an indwelling urethral catheter. The medical consultant concurred in the opinion that operative risk would be justifiable. After 7 weeks of drainage with supportive therapy, repeated small blood transfusions, high vitamin and high protein diet, the patient was scheduled for operation. The bladder was exposed suprapubically, and opened. The bladder mucosa was remarkably normal in appearance. A ureteral catheter was passed up the left ureter and left inlying. The diverticulum was packed with a gauze strip and easily mobilized. It was then excised in toto. The defect was repaired and the bladder closed around a suprapubic catheter. When the specimen (fig. 2) was examined, a surprising feature was that only a small plaque-like lesion, approximately 1 cm. in diameter, remained of the tumor. Apparently the papillary processes had sloughed away or had been removed with the cystoscopic forceps. The tumor had not invaded the wall grossly or microscopically (fig. 3); however, there was marked marginal lymphocytic infiltration which was considered to represent a pre-invasive stage.

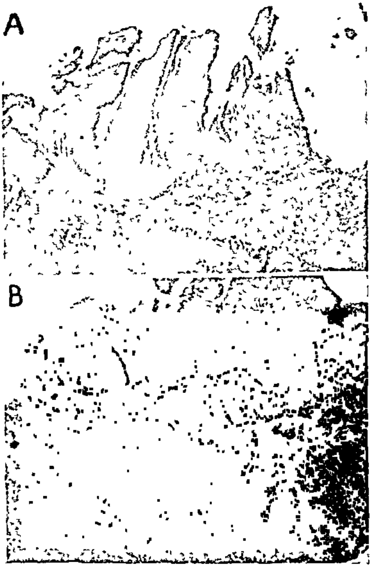

Fig. 3. *A*, Low power photomicrograph; *B*, high power. (Courtesy of Army Institute of Pathology.)

Healing was delayed in spite of supportive therapy, and there was persistent drainage from the lower angle of the wound. Inasmuch as the tumor bearing area had been removed completely, there did not appear to be any indication for radiation therapy.

Six and one-half weeks after the operation, the patient suffered another cerebral accident and expired 1 week later.

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CYSTOMETRY, AND THE TREATMENT OF VESICAL DYSFUNCTION IN PARAPLEGIA[1, 2]

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INTRODUCTION

The major urologic problems encountered in the care of patients with spinal cord injuries arise, either directly or indirectly, from interference with the normal innervation of the bladder. A prominent exception is the tendency to urinary lithiasis which is frequently exhibited by patients undergoing long periods of muscular inactivity for any reason; but even this is, in these cases, notably enhanced by the stagnation and infection resulting from the vesical dysfunction. It is, of course, well known that vesical function which is normal, or clinically indistinguishable from normal, is restored spontaneously in a significant proportion of cases of spinal cord injury, even though paralysis of the extremities may remain. It is probably true, as well, that if genuine recovery of bladder function is to occur, it will occur relatively early, perhaps as soon as spinal shock has passed. But spinal shock is itself a phenomenon of variable duration. Sensory and motor return in the extremities are seen 18 months or more after injury, and although visceral return may not be anticipated after so long an interval, it is difficult to find logical justification for establishing an arbitrary time limit beyond which no prospect remains but permanent suprapubic drainage.

The chief value of a suprapubic cystostomy is implicit in its being established early, when the patient is unable to empty his bladder unaided, and when external circumstances render any other form of drainage dangerous or impracticable. Drainage through a surgically created fistula is not a substitute for normal function. It is a means, not the best but sometimes the most expedient, of carrying the patient through the early phase of his treatment. It should be discontinued as soon as the means and facilities are available for instituting tidal drainage, and before the inevitable contraction of the bladder has reached an irreversible state. Its permanent use should be reserved as a last resort for those cases in which every other resource has failed to yield a satisfactory type of voiding.

It is perhaps true that a permanent suprapubic tube may be less inconvenient than what is generally known as an "automatic bladder." This designation, a particularly unfortunate one, is generally applied to those bladders which empty themselves periodically, and more or less completely, but independently of any voluntary control. They might more correctly be termed reflex bladders since they are activated largely if not entirely by reflex mechanisms. Fortunately, the reflex bladder can in many instances be brought under a form of voluntary control sufficiently effective to avoid major inconvenience.

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[2] Read at annual meeting, Mid-Atlantic Section, American Urological Association, Washington, D. C., March 22, 1947.

THE PHYSIOLOGY OF MICTURITION

The autonomic nervous system. Visceral control is exercised largely through those parts of the nervous system which, although not entirely divorced from the will, carry out the major part of their activities without benefit of voluntary direction. These nervous pathways and their associated nuclei and ganglia are collectively termed the autonomic nervous system, which is divided into 2 sets of pathways, the sympathetic and the para-sympathetic. The former comprises the thoraco-lumbar, and the latter the bulbar and sacral outflows. The efferent, or to use Gaskell's terminology, the excitor neurons of the sympathetic pathway are generally situated in the various sympathetic ganglia, while those of the parasympathetic system have tended to move even more peripherally and are usually found in the ganglia situated in the walls of the various viscera which they innervate. The motor nerves to the bladder and urethra contain efferent fibers from both the sympathetic and the parasympathetic, but the latter are the essential nerves of micturition. The frequently stated theory of their antagonistic action on the detrusor muscle and the internal sphincter has now been largely discarded. Although there seem to be sympathetic inhibitor fibers to the detrusor, the sympathetic supply is not essential to micturition, and its interruption has no appreciable effect upon this function. The opening of the so-called internal sphincter, which takes place reciprocally with the contraction of the detrusor muscle, is a mechanical action dependent upon the arrangement of the longitudinal muscle fibers of the bladder wall which are continuous on to the urethra. If there is any nervous component at all in this reciprocity, it must be mediated through the ganglia of the vesical plexus itself, since it may take place even when all connections with the central nervous system have been severed. There is no need, therefore, to postulate a dual control, depending upon the balance of antagonistic impulses. Efferent sympathetic fibers supply the trigonal muscle, the posterior urethra, the seminal vesicles, the ejaculatory ducts, and the prostatic musculature. All of these are mesodermal tissues and are concerned with the motor aspect of the sexual function. The blood vessels of the bladder wall are also supplied by sympathetic fibers. The detrusor muscle is derived from the cloacal membrane and receives its motor innervation from parasympathetic fibers from the second, third and fourth sacral segments, which pass through the sacral nerves.

The external sphincter is supplied by the pudendal nerves, which are derived from the third and fourth sacral segments and are part of the voluntary nervous system.

The sensory nerves of the bladder. Afferent fibers from the bladder and urethra course through the sympathetic and parasympathetic pathways, as well as through the pudendal nerves, conveying a variety of sensations which is unusual among hollow viscera. The bladder is sensitive to both superficial and deep stimuli, the latter being those of muscle stretch. Its mucosa responds, in slight degree at least, to heat, cold, and tactile stimulation, and is highly sensitive to pain. Some localization of the point stimulated is possible. Since afferent fibers in the sympathetic nerves may enter the spinal cord as high as the ninth dorsal segment, it is possible for a patient with transection of the spinal cord below this level to retain some awareness of pain and distension, a point of some importance in bladder training after such injuries. The urethra and, in the male, the corpora cavernosa are also supplied with afferent somatic fibers which are transmitted through the pudendal nerves.

Bladder tone. All contractile tissues, throughout the body, are in receipt of a constant stream of impulses from the central nervous system, to which in turn they contribute a like stream of afferent impulses. A state of balance results, and the influence of the central nervous system is called tonic. Relations of the organ so influenced to the body as a whole are termed postural; posture is then an active response of an integrating nervous system to forces tending to disturb the configuration of the part. The bladder, far from being an inert elastic sac, exhibits this postural tone in full measure, assuming a new configuration whenever its contents increase or decrease. The tonic control of its musculature is thought to be exercised by mechanisms similar to those controlling tone in striated muscle.

From experimental evidence, it appears that bladder tone is regulated from centers near the cephalic border of the hind brain, which are in turn subject to impulses from the motor areas of the cerebral hemispheres. The vesical musculature is also influenced by impulses arising in autonomic centers in the hypothalamus, through which psychic influences are probably mediated. Descending influences from all these higher centers reach the bladder through the spinal reflex centers in the second, third, and fourth sacral segments and it is logical to believe that final integration takes place at these levels. It is likely that the sympathetic inhibitor fibers, previously noted as having no direct part in the act of micturition, are a factor in maintaining this tonic balance.

It is obvious, however, that the influence of the higher centers upon vesical function involves more than the mere maintenance of a static tonus. They integrate and co-ordinate, with a high degree of accuracy and efficiency, all the contractile phenomena exhibited by the bladder and urethra. The purely reflex bladder of spinal cord injuries has lost more than direct voluntary control. However satisfactory a clinical approximation of normal function it may achieve, it cannot develop the exquisite capacity for adjustment and efficient action which is observed in the intact mechanism. Thus, injury to the nervous mechanism results not only in simple loss of function, but in positive dysfunctions caused by the released activities of undamaged nervous centers, previously subject to constant control.

The act of micturition. From the foregoing, it will be evident that although the bladder be termed a reflex organ, and micturition a reflex act, these terms are but relative. In man, purely reflex activity of the bladder is observed only in infancy, or after the interruption of pathways above the reflex arc. This concept is essential to an understanding not only of the normal act of micturition, but to those alterations which may be anticipated after injury of the spinal cord. The most striking of such alterations is the loss of voluntary control, and a discussion of the probable nature of this control offers a convenient point of departure for the investigation of the normal mechanism of micturition.

The human bladder reacts to distension by contraction of its muscular wall. But as soon as the distension ceases, or even during its course if it be slow and gradual, there occurs a remarkable adaptation in the form of a lengthening of the individual muscle fibers with a consequent dilatation of the viscus. The response to the so-called stretch reflex is therefore biphasic, and the bladder maintains, as one observer described it, a constant gentle grasp on its contents. While the bladder is being gradually filled, there is a gradual slow increase in intravesical pressure; when the fill is interrupted the pressure drops, indicating the adjustment of the bladder's configuration to its contents at that moment. As the distension increases, however, the capacity of the bladder to adapt itself by further dilatation diminishes. Eventually, a point is reached at which in the absence of inhibition, a further stretch stimulus brings about forceful contraction of the detrusor with consequent emptying. In the infant such inhibitions do not occur, and the emptying contraction is unimpeded.

In the normal adult, as demonstrated in the classical experiments of Denny-Brown and Robertson, this reflex contraction is controlled by the restraining effect exerted by higher centers. The site of impact of this inhibition is probably upon the efferent neurons in the sacral segment of the cord, and it is so effective that the spontaneous nervous discharges which produce vesical contraction can be inhibited with ease. At low volumes, this mechanism operates below conscious levels, gradually intruding upon consciousness as volume increases. Perceptible sensation is produced only when the contractions pass a certain threshold of intensity. Restraint of micturition is thus in the nature of a direct inhibition. But since it has been demonstrated that voluntary micturition is entirely secondary to an active contraction of the bladder, and since this can be evoked only by the stimulus of stretch, it follows that true voluntary initiation of micturition does not occur. It is not denied that willed efforts to urinate can bring about contractions of the detrusor, which develop with only a brief period of latency, and even in the absence of extrinsically applied stretch stimuli, such as may be produced by increased intra-abdominal pressure. The mechanism in this event is indirect, however, and consists essentially in the voluntary withdrawal of inhibitory impulses. It is concluded therefore, from the direct nature of the restraint and the indirect nature of facilitation, that voluntary control is effected by variations in conscious or unconscious inhibitions of the spontaneous reflex mechanism. It follows, as Kuntz has pointed out, that voluntary control of micturition undoubtedly is facilitated by a normal functional balance of the sympathetic and parasympathetic nerves. This has already been suggested in the discussion of bladder tone.

The parts played by the internal and external sphincters in voluntary and reflex micturition have been the subject of intense clinical and experimental investigation and no little controversy. Although the term internal sphincter is here retained for convenience, because of its familiarity, there is in fact no true sphincter at the vesical orifice, in the sense of a complete well marked ring of muscular tissue. The trigone, which is embryologically distinct from the detrusor portion of the bladder wall, is formed by a continuation of the ureteral musculature and itself continues along the posterior wall of the urethra. The nerve close down on its contents, bringing about an increased intravesical pressure which is immediately reflected by the sensitive water manometer. It must be recalled that the only known *stimulus to detrusor contraction is stretch*, a dynamic rather than a static phenomenon. The increases in pressure are a function not of the absolute volume of bladder contents but of additional increments of volume. With the volume held constant the pressure drops as the muscular wall adapts its configuration to its new content. In other words, the intravesical pressure after a preliminary rise drops again to a base line after each added increment. As the total volume increases, this base line gradually rises, eventually reaching the point at which further accommodation does not occur and the degree of stretch is sufficient to stimulate an emptying contraction. This illustrates most beautifully the bi-phasic character of the response of smooth muscle described as the stretch reflex, and is evidence as well of the control of tonus and coordination exercised by higher centers, for bladders which have suffered interference with their innervation display definite changes in this process of accommodation.

The normal bladder makes this adaptation with remarkable speed and smoothness. As the fluid runs in, there is a gradual even rise in pressure, with an almost immediate drop to the base line as soon as the flow is interrupted. In fact, with the slow rate of flow used during this series of observations, some bladders appeared to be able to make their adjustment even as the fluid ran in, so that there was no perceptible drop as the fill was discontinued. Seldom was the drop more than 5 cm. of water, and only rarely as much as 8 cm.

With disturbances of innervation such as occur with spinal cord injury, this ability of the vesical wall to adapt its configuration to a varying content may be gravely impaired or lost entirely. The immediate reaction of the bladder wall to the inflow of fluid is then so exaggerated that the slow addition of only a few cubic centimeters may bring about a rise of pressure of as much as 35 cm. Such marked pressure changes may occasionally be associated with leakage around the catheter and so were at first confused with what might be called emptying contractions. Since the latter do not necessarily succeed in emptying the bladder, the distinction may seem arbitrary, but it is, in fact, of some physiological importance. An emptying contraction may be defined as a more or less co-ordinated wave of muscular contraction brought about by the stimulus of stretch and resulting in a well sustained expulsive effort. Cystometrically, it is characterized by a rapid but smooth rise in pressure to a point at which it is held until fluid escapes past the bladder neck, when it drops sharply. When, because of obstruction at the vesical neck or insufficient detrusor force, there is no such leakage, the pressure drops, after a variable interval, smoothly and uninterruptedly to the base line. To avoid confusion, these were described as involuntary contractions regardless of whether or not they brought about expulsion of the bladder's contents. Whatever they may be called, they are easily distinguished from the irregular increases in pressure just noted. With the latter, the fluid level in the manometer rises jerkily and, instead of holding steadily at its peak, swings up and down through an excursion of as much as 10 to 15 cm. Only rarely is it associated with passage of fluid through the internal orifice, probably because there is seldom a sufficiently well maintained or co-ordinated contraction to draw open the bladder neck.

Most characteristic is the delay and irregularity of the fall in pressure to its base line. Although the regular procedure was to interrupt the fill in order to give the vesical wall every opportunity to accommodate itself, the drop was slow, and frequently interrupted by intercurrent rises. When the patient was asked to strain, as usual, it sometimes happened that the fluid level following the strain fell to a level a few centimeters below that noted immediately before; the curve was then plotted to the lower reading. In observing this entire phenomenon, it was difficult to escape an impression of inefficiency and inco-ordination, particularly as compared with the steady behavior of normal or more nearly normal bladders, so that during the course of the work the terms stable or unstable crept into daily use. It was further noted that an unstable bladder, so-called, remained so at every level of fill, although the fluctuation became less marked as the volume and pressure rose, while the bladder which adjusted itself speedily to the first increment continued to do so until its capacity was reached.

Since the impulses controlling tone and co-ordination are probably integrated at the level of the sacral reflex centers, it is to be expected that lesions at this level will result in the most serious loss of function. With such injuries, the resulting bladder is called autonomous, since it has been severed from its connections with the central nervous system. The reflex arc upon which its contractions must then depend is the short one mediated through its intrinsic ganglia. There is little or no co-ordination and no tonic adaptation. Cystometrically, these bladders exhibit an extreme degree of instability; they are markedly hypertonic and show frequent involuntary contractions which do not succeed in expelling the contents. Clinically, they are characterized by small capacity, high residual, and frequent involuntary voidings of small quantities of urine. They are of all types of neurogenic bladder the most distressing to endure and the most difficult to treat.

With injuries at higher levels of the spinal cord, which leave intact the reflex centers in the sacral segments, the degree of vesical dysfunction depends not so much upon the precise level as upon whether or not the tracts through which impulses travel from higher centers to the bladder are interrupted. Similarly, the severity of the injury, insofar as it affects vesical function, is of less significance than its specific effect upon the fibers of these tracts. Conceivably, a complete transection may leave a better result than an incomplete lesion which leaves iome fibers intact while destroying others. For there can be no satisfactory sntegration in the sacral segments when the impulses arriving there are irregular and confused, and a completely reflex bladder may be more amenable to corrective training than one subject to such stimuli. Since most of the tonic control exerted upon the sacral reflex centers is inhibitory in character, it follows that the reflex bladder will generally be hypertonic, and this is borne out by cystometric studies. The exaggerated tonus may be further enhanced by infection, calculus, irritation of the catheter, spasm of the skeletal muscles, and by the contracture consequent upon prolonged continuous drainage, whether by catheter or suprapubic tube. The atonic bladder is usually characteristic of interruption of the afferent half of the reflex arc, such as occurs in tabes, and will not often be found in cases of spinal cord injury.

Cystometry may generally be expected to reveal the state of tonus and the presence or absence of involuntary contractions. It cannot by itself identify nor evaluate the factors contributing to tonic alterations. Neither can it localize the neurological lesion, nor is it reasonable to expect it to do so, although it may be helpful in determining whether or not a transection is complete. As carried out in this series of cases, it also revealed the extent to which intravesical pressure could be raised by voluntary straining, and provided the occasion for an accurate determination of vesical sensation at various stages of filling, both important considerations in the method of treatment pursued.

TREATMENT

The treatment of neurogenic vesical dysfunction in paraplegia is fundamentally a problem in rehabilitation. It must develop the fullest utilization of all remaining function, along with such substitutes as may be available for that part of the function which has been lost. In the case of vesical dysfunction as found in paraplegia, it involves training the reflexly acting viscus to its maximum efficiency and superimposing upon this some type of control to replace that lost through impaired innervation. The rationale of an approach to the problem is comprehended in the following observations:

1. A reflexly acting bladder can in many cases be brought to a serviceable degree of efficiency, in respect to its capacity and its ability to empty itself.
2. The loss of control in these cases is essentially a loss of the inhibitory influence exerted by the higher centers.
3. The effective stimulus to detrusor contraction is stretch. Given a certain degree of vesical distension, the degree of stretch necessary to excite an emptying contraction may be produced by pressure applied voluntarily to the exterior of the viscus, usually by abdominal straining. Thus the patient retains the capacity to facilitate the initiation of micturition. It will be recalled that with an intact nervous system voluntary micturition is brought about largely by the withdrawal of inhibitory impulses. Since these are absent in the paraplegic, a sufficient degree of stretch is theoretically all that is required to initiate micturition, and this, in fact, is what occurs when the bladder empties reflexly.
4. This ability to initiate voiding voluntarily, coupled with an awareness, either through sensation, or by timing if sensation is absent or unreliable, of the approaching limit of bladder capacity, enables the patient to anticipate involuntary reflex micturition.
5. If, as is often the case, the bladder's capacity can be established at a reasonably consistent level, the patient will be able to keep dry.

Proceeding from these fundamental considerations, the ideal of treatment may be stated as comprising four main objectives, which will be considered in order.

1. The establishment of urethral voiding.

2. A bladder of sufficient capacity to act as a reservoir for convenient intervals and with reasonable consistency.
3. A bladder which is capable of emptying itself completely or almost completely.
4. A sufficient degree of control to avoid involuntary escape of urine.

Urethral voiding is an obvious prerequisite to any approximation of normal bladder function, and this involves the closure of all fistulas, be they deliberate or accidental. The literature, particularly that of a few years back, contains references to indications for permanent suprapubic drainage, and it is true that in our present state of skill and knowledge there are occasional patients who will have to be left with permanent adventitious drainage of one sort or another. But an occasional unexpectedly good result in this series has encouraged the conviction that no patient should be condemned in advance to this prospect. Nor may it be forgotten that the more nearly the bladder function approaches normal, the stronger the likelihood that the upper tract will remain healthy.

The accidental fistulas are those which develop as the result of infection. These are almost invariably periurethral and most often emerge in the region of the penoscrotal junction. They are sometimes associated with urethral diverticula which require plastic surgery if they do not drain adequately into the urethra.

A fair proportion of suprapubic sinuses will close spontaneously during urethral catheter drainage, particularly if the fistulous tract enters high on the bladder wall. Unfortunately, most of those encountered in this group were close or even adherent to the symphysis pubis, and these, if they do close, are apt to reopen with the slightest strain. If firm, spontaneous closure does not occur in 2 or 3 weeks, definitive surgical repair is indicated, as it is in practically all urethral fistulas.

Rehabilitation of vesical function depends next upon an adequate bladder capacity. For practical purposes, this should be not less than 8 ounces, and 10 is better, although a bladder which retains no more than 6 may be fairly satisfactory if there is good control. Patients should not be encouraged in their sometimes enthusiastic efforts to demonstrate how much they can void at a time. No useful purpose is served by a capacity exceeding 12 ounces. A greater distension may encourage ureteral reflux when the ureteral orifices are incompetent, as is sometimes the case, and the task of contracting around and expelling too large a volume of fluid may place too heavy a burden upon a detrusor already embarrassed by disturbed innervation.

Provided that irreversible changes have not taken place in the bladder wall, it is often possible, although not always easy to increase the capacity of a contracted bladder to a useful level. This is accomplished by gradual and gentle distension carried out over a considerable period of time, and to this end tidal drainage has been most useful. Properly carried out, it provides an easily controlled method of procuring this gradual distension, while at the same time helping to keep the bladder clean and free from infection. Abrupt and forceful distension defeats its own purpose by stimulating the stretch reflex. Quite as important as the actual capacity is its consistency, that is, the bladder's ability unfailingly to accommodate this amount before going into an involuntary expulsive effort. An organ which may hold no more, for instance, than 6 ounces but which is never stimulated to emptying by a smaller content, is a better subject for training than one which, although it can carry 12 ounces at times, is equally likely to empty reflexly at 4 or 5. Such consistency may be more difficult to achieve than a mere increase in maximum capacity and will almost certainly take longer.

The elimination of residual urine or its reduction to a neglibible quantity is of paramount importance, not only in respect to vesical function but because it constitutes a dangerous source of infection to the rest of the urinary tract. A reflex bladder may empty itself completely; but frequently, and despite its hypertonicity, it will carry a residual urine of significant amount. There are probably two main explanations of this apparent paradox. First, there is the faulty co-ordination of the contractile impulses, most marked in the autonomous bladder but exhibited in varying degrees with injury at higher levels of the cord as well. In some cases, there is actual insufficiency of the detrusor force. Second, there must be considered the development of obstruction at the bladder neck. As Emmett, among others, has indicated, there is no true sphincter at the internal orifice. The so-called bladder neck is, in effect, the edge of the detrusor muscle, and as such shares in the hypertrophy associated with increased tonus and constant ineffectual contractions. Infection and secondary fibrotic changes will enhance the obstruction thus produced. Even when no declivity can be demonstrated cystoscopically, these changes may be sufficient to impede the normal reciprocal opening of the internal orifice on detrusor contraction. See figure 1.

Muscle tissue in general is susceptible of improvement in strength and co-ordination under the influence of controlled use, and all planned therapeutic exercise is based upon this premise. The smooth muscle of the bladder is no exception and as a means of providing such controlled rhythmic exercise, in simulation of normal function, tidal drainage is the best device available. When it is discontinued, or even during its continuance at night while the patient is up and about by day, the catheter is left in, with a clamp attached, the clamp being opened at intervals approximating those at which the bladder is emptied by siphonage, with due allowance for the fact that no fluid is being run in. And when, finally, the catheter is removed, the patient is trained to void at corresponding intervals. As the capacity of the bladder increases, these intervals will of course be lengthened proportionally.

Transurethral resection is indicated for demonstrable obstruction at the bladder neck, and in carefully selected cases will bring about a sharp reduction in the amount of residual urine, or its complete disappearance. In view of the nature of the disease, as previously described, it is not sufficient to resect only a small arc at the floor of the bladder. As Thompson has suggested, the procedure must include the entire circumference of the internal orifice, and, if insufficient tissue is removed at the first attempt, there need be no hesitancy about repeating it. Although, in this series, the indications for transurethral resection have not been so broad as those advocated by Emmett and Thompson, the usefulness of the operation is not limited to those cases in which gross obstruction may be observed cystoscopically. Whenever there is a persistent residual urine associated with what appears to be a sufficient and satisfactory detrusor force, as demonstrated cystometrically, resection is amply justified

With a bladder which is intact, reasonably clear of infection, possessed of a useful capacity, and capable of emptying itself completely or almost completely, the effort is made to establish control by training the patient to initiate voiding voluntarily at appropriate intervals. In the absence of inhibitory power this provides, after adequate training, an effective method of avoiding involuntary micturition. It is apparent that some means must be available whereby the patient can be aware that the bladder is approaching its capacity. About 70 per cent of the patients in this series retain some degree of vesical sensation in association with vesical filling. This may manifest itself as a relatively normal desire to void, a sense of pressure in the lower abdomen, suprapubic or more generalized abdominal pain, or pain and burning in the penile urethra. It is important to differentiate sensation associated simply with distension from that which accompanies a contraction, since the latter occurs too late to be usefully exploited. The former, whatever form it takes, can usually be recognized at levels of filling well within the bladder's capacity, providing a means whereby the patient can train himself to an awareness of his bladder's distension and its approximate degree. Not infrequently there are other manifestations of a full bladder, presumably provoked by autonomic stimulation, such as sweating, chills, goose

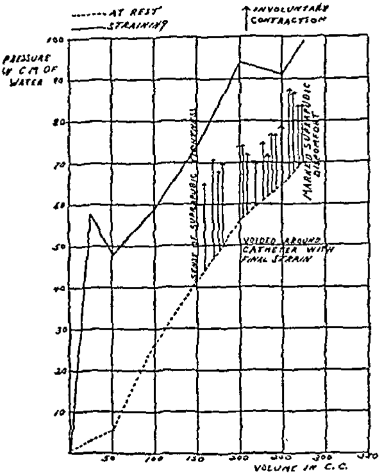

FIG. 1. Cystometrogram, suggesting indication for transurethral resection. Level of injury, D8. Hypertonic bladder with frequent ineffectual contractions during filling. Good pressure on straining, but no opening of internal sphincter until extreme pressure had been reached. Residual urine 225 cc. Following resection, residual urine was eliminated.

pimples, or headache. These usually anticipate the bladder's involuntary emptying by so short an interval as to have little value as signals.

The group of patients in whom sensation is absent or unreliable must rely upon timing, and regulation of fluid intake. This is more difficult and not so satisfactory, but quite practicable in the case of an intelligent and co-operative patient, who is able, after some experience, to adjust the frequency of his voiding to the amount of fluid he takes. The same method is applicable to all patients at night, although most will require to be aroused at least once to insure a dry bed.

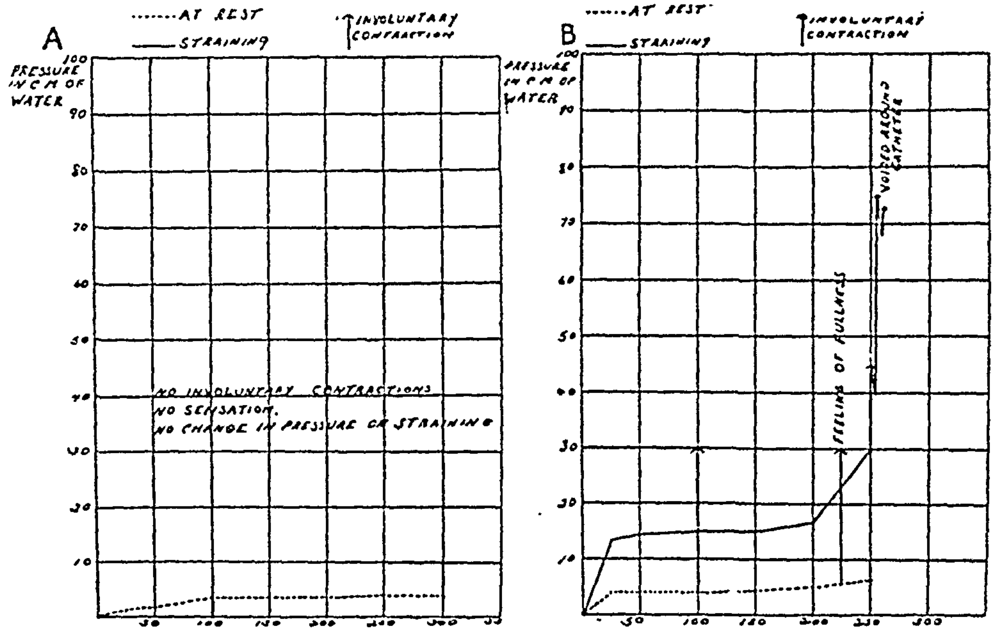

FIG. 2. *A*, cystometrogram made 6 weeks after injury at level C5 and 6. Spinal shock still present. Atonic bladder. *B*, same case 4 months later after treatment by tidal drainage. Some recovery of bladder tonus; occasional involuntary contraction; return of bladder sensation; fairly good straining pressure with emptying contraction stimulated by strain at fill of 250 cc. Patient now voiding per urethram; capacity 250 cc, residual 30 cc; can initiate micturition voluntarily by straining.

All normal individuals have encountered the difficulty of trying to urinate when the bladder was not sufficiently full. But if it be moderately distended, even though not to the point of having produced conscious desire to void, micturition can readily be initiated by straining. With this there are probably associated an elevation of the perineum and the withdrawal of inhibitory impulses, the latter an unconscious phenomenon. The straining results in increased intra-abdominal pressure which, impinging upon the wall of the bladder, produces a sufficient rise in intravesical pressure to initiate the stretch reflex. Thus the straining itself does not primarily initiate micturition, but begins a train of events leading up to detrusor contraction. This in turn is associated with opening of the internal orifice and the escape of urine. Unless this opening takes place even most considerable pressures will not bring about voiding, as pointed out by Denny-Brown. During cystometry it is sometimes possible to demonstrate a brief but perceptible latent period between the straining effort and the resultant active contraction of the bladder muscle. Once the act of micturition has begun, however, further straining or manual pressure may usefully augment a detrusor force which would otherwise be inadequate to discharge the contents of the bladder completely. To enhance this effect, or to increase the intra-abdominal pressure originally generated, a simple type of abdominal belt has sometimes been found helpful, and in at least 1 case spelled the difference between success and failure. See figures 3 and 4.

Straining is not the only method of initiating micturition although by far the most reliable. Trigger mechanisms, often described and sometimes, although less frequently encountered, may occasionally be exploited. Generally, however, they are neither consistent nor dependable enough to be of much assistance.

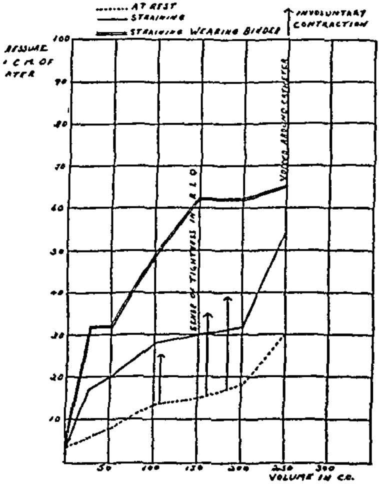

FIG. 3. Effect of wearing abdominal binder on pressure produced during straining enabling patient to initiate voiding and empty bladder. Level of injury D6. Residua urine without binder 225 cc; with binder 10 cc.

In spite of the most carefully planned treatment and its most carefully considered application to individual cases, it cannot be expected that equal or even satisfactory results are to be obtained with all patients. The most favorable may be anticipated when the reflex centers in the spinal cord have been left intact. A bladder entirely deprived of communication with the central nervous system and dependent upon the intrinsic innervation of the vesical ganglia is at a disadvantage which no known treatment is likely to overcome entirely. Regardless of the level of spinal cord injury, there are a great number of other factors which influence the course of treatment. The urologic complications are beyond the scope of this discussion and will not be considered at this time. Among the others, two of the most important are decubital ulcers and somatic spasm. Few of these patients escape bed sores and if they are severe it is generally necessary to defer definitive attempts at bladder rehabilitation until they have healed. During the healing process, however, tidal drainage may be employed to advantage for retention or incontinence or both, constituting at the same time the first stage in retraining the detrusor. Spasm is at times no obstacle to vesical recovery, at others a serious impediment. In the latter instances there may be incontinence during the spasm. Although this has been explained as a manifestation of a mass reflex, it is more probable that the voiding follows upon increased intra-abdominal pressure due to the flexion spasm. This occurred frequently during cystometric observations, and the pressure changes could be readily followed. Voiding did not take place unless there was an associated detrusor contraction which could be identified by its known characteristics, and often by a period of latency as well.

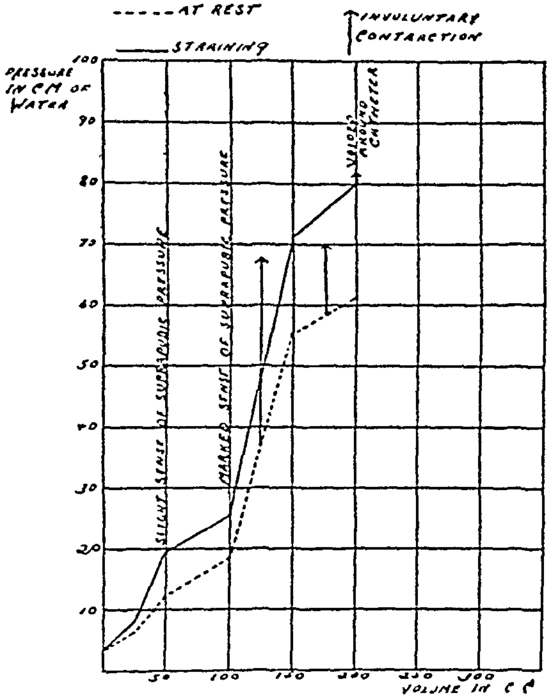

FIG. 4. Extreme hypertonicity in reflex bladder; injury level C3. After repeated intervals of tidal drainage over a period of 7 months, patient achieved voluntary urethral voiding, and is being trained in control.

Another annoying incident is the participation of the muscles making up the external sphincter in the spastic reaction. If this occurs during micturition there is an abrupt cut-off effect, and since the inhibition of the detrusor normally associated with this may be absent, considerable discomfort may result. Fortunately, this is a transitory phenomenon and little harm is done, although the patient may be unable to resume voiding until more urine has accumulated in the bladder.

There are other discouragements. Tidal drainage for all its great value, is no panacea. The apparatus, despite the semi-automatic character of its action, requires close supervision, and although it offers an improvement in bladder hygiene, the urine invariably becomes infected. It is true that the vast majority of the cases studied were those with old injuries with pre-existing urinary tract infection of long standing, but the few acute cases among them also developed infected urine within a short time. Munro differentiates between infection and bacteruria, but it is a nice distinction upon which one is unwilling to lean too heavily. Even in the absence of any clinical evidence of urinary infection, the continued presence of organisms, often of the urea-splitting variety, in the urine is a disquieting fact. Routine prophylactic chemotherapy has been considered, and tentatively employed in a few instances, but it is difficult to apply practically in these cases, and there is always the risk of developing resistant strains which would mitigate against the successful use of the drugs during an acute clinical exacerbation. In none of the cases here discussed was tidal drainage employed while a suprapubic sinus existed. It did not appear likely that any success in the retraining of the detrusor muscle could be achieved and the hygienic effect could be as readily obtained with intermittent drainage through a simpler apparatus. See figures 5 and 6.

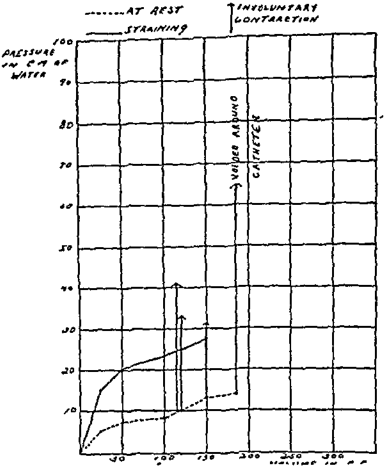

Fig. 5. Characteristic involuntary reflex bladder. Level of injury D7. Cystometrogram made following surgical closure of long-standing suprapubic sinus. Patient is continuing on tidal drainage and bladder training.

Another constant hazard of any prolonged catheterization is urethral infection with its attendant complications. Periurethral abscess or fistula has been observed only once during tidal drainage in patients not so affected previously, but epididymitis has been frequent. The only extenuating aspect of this is that it is also frequent among those who do not wear a catheter, bearing in mind that all but the acute cases were already harboring lower urinary tract infection when first seen. It is a fact, moreover, that certain other devices employed to alleviate incontinence, such as penile clamps or condom-coupled tubes, are also contributing agents to urethral infection, and may produce edema and excoriation of the penis as well.

The same factors which act to impede or retard the achievement of satisfactory results may, if they recur, cause a regression from results already achieved. Prominent among these are infection, toxemia, and general debility, in whatever part of the body or from whatever cause, as the case may be. But by the same token, the establishment of satisfactory urethral voiding in a patient who is out of bed and active constitutes a significant safeguard against these eventualities.

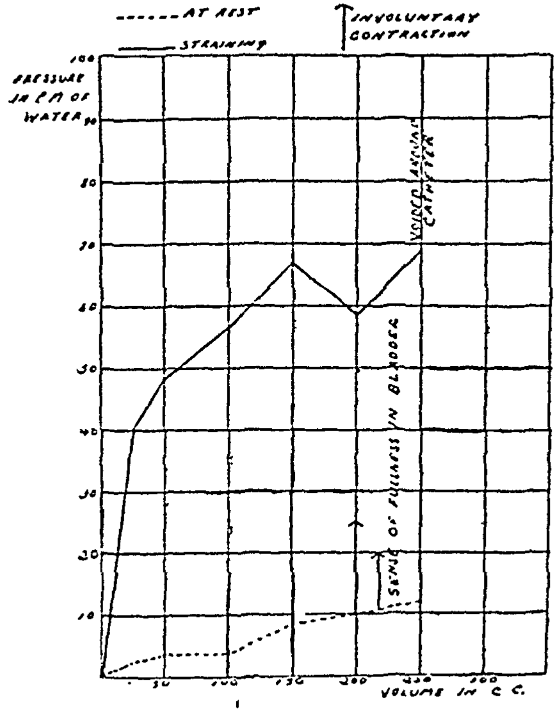

FIG. 6. Reflex bladder with capacity of 300 cc, residual urine 10 cc, and good pressure on straining. Level of injury D11. Patient voids per urethram, can initiate micturition before reaching capacity, as shown on graph, and has good control. Example of good function achieved with no particular treatment save habit training.

A good follow-up, and the co-operation of the attending physician after the patient has left the hospital are highly desirable for this reason.

Finally, but by no means least important, there is need for the whole-hearted understanding and co-operation of the patient. The program here outlined calls for courage and patience and a willingness to try hard for results which may appear meagre and slow in coming. In spite of every effort at education, there are a few who remain recalcitrant, who cannot or will not realize that the end may be worthy of the means. The most convincing missionary work is done by those who have tried and succeeded. For success, or at least relative success, has been frequent enough to encourage the conviction that this is a reasonable approach to the problem.

SUMMARY

The bladder is a reflex organ upon which has been superimposed a number of controls exerted by the higher nervous centers, which are largely inhibitory in character, with probably an added factor of coordination. The normal bladder manifests a striking capacity to adapt its configuration to changes in the volume of its contents. Detrusor contraction is stimulated by stretch only, and is associated with a reciprocal opening of the internal orifice which is independent of central nervous control. Inhibition of micturition is a direct mechanism; facilitation is indirect and is effected by withdrawal of inhibitory barriers to reflex contraction.

The reflex centers for vesical function are located in the second, third, and fourth sacral segments of the spinal cord. The efferent supply to the detrusor passes through parasympathetic pathways. Interruption of the sympathetics has no effect upon micturition. The afferent fibers pass through both parasympathetic and sympathetic channels, some of the latter entering the cord as high as the ninth dorsal segment.

Cystometry provides a valuable means for the study of the normal or pathological physiology of the bladder.

The treatment of neurogenic vesical dysfunction after spinal cord injury should not be considered as completed when reflex involuntary voiding has been established. A program of rehabilitation is suggested which, in a considerable number of cases, will result in urethral voiding, little or no residual urine, a useful bladder capacity, and a reasonable degree of voluntary control. The methods employed include closure of urinary fistulae, tidal drainage, training of the patient to initiate voiding at suitable intervals, and transurethral resection in suitable cases.

My sincerest gratitude is due to my colleagues, Dr. R. C. Bunts and Dr. L. W. Holladay, for their unselfish help and suggestions. The burden of the clinical work represented in this study was shared equally by all three of us, and although the author bears responsibility for any opinions herein expressed, the program suggested is the result of joint effort and enterprise.

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A NEW BLADDER INSUFFLATOR: ITS USE IN TUBERCULOUS CYSTITIS[1]

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The purpose of this paper is to describe a new instrument for the insufflation of powdered medication into the bladder, and to report the results of its use in a series of patients with chronic tuberculous cystitis.

There are many measures and procedures which are helpful in the treatment of tuberculosis of the bladder. However, these are not always successful and there are patients who are not benefited by treatment. In an effort to help this group, it was decided to explore the possibility of treatment by bladder insufflation. From the available literature it appeared that this procedure had not been utilized previously.

About a year ago the first instrument was devised.[2] This proved to have many drawbacks and several additional models, with necessary modifications, were made, resulting in the present instrument which seems fairly satisfactory (figs. 1 and 2).

DESCRIPTION OF INSTRUMENT AND METHOD OF USE

The instrument consists of a slender metal tube (adapted to a size 24-F Brown-Buerger cystoscope sheath) and an atomizer. The medium-sized cystoscope was chosen since it passes through the urethra into the bladder with less pain and difficulty. The convex type of cystoscope is more often used as it drains the bladder well when inserted, and after drainage is complete, it is rotated so that the opening points upward into the bladder. The rotation limits further wetting of the interior of the sheath and permits the insufflated powder to reach the greater part of the bladder wall. The tube is fitted with the conventional lock arrangement at the proximal end to secure it in the cystoscope sheath. It is closed at the tip, but near the end there are several large openings for the passage of the insufflated medication and air into the bladder. The tube is carefully fitted in the center of the sheath, away from the wall, so as not to touch the distal end of the sheath, and it is held in this position by supports which are constructed to allow the free passage of urine and air in the sheath. This is done in order to keep the tube as dry as possible. The tube extends from the proximal end of the sheath at an angle, and a rubber tube is attached which connects with the atomizer and receptacle for the medication. A second rubber tube is for drainage of the sheath.

To perform insufflation, the cystoscope is passed to the bladder. The obturator is withdrawn and the bladder drained of urine. Cystoscopy may then be done before the insufflation if it is desired to observe the interior of the bladder or to watch the progress of the treatments. After draining the bladder, the sheath is rotated with the opening upward. The insufflator tube is passed into the sheath and locked in place. The rubber bulb is attached and the tube and sheath are dried by expressing several bulbfuls of air through the apparatus. The success of insufflation rests largely with the state of dryness of the tube, and

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., July 3, 1947.

[2] I wish to thank Mr. Fred Wallace, president of the American Cystoscope Makers, Inc., New York, N. Y., for his help and suggestions in the development of the instrument.

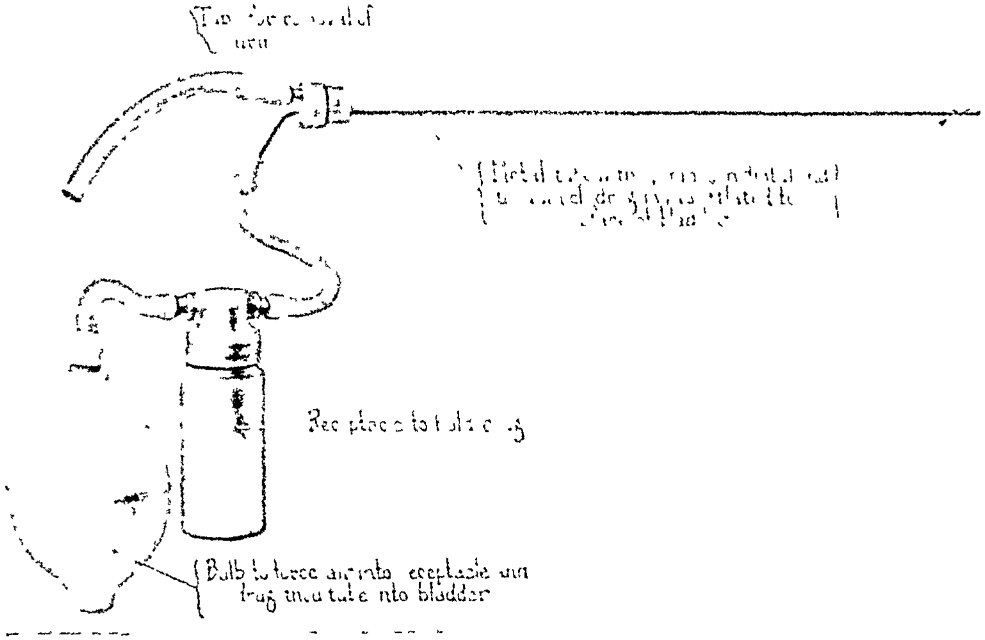
Tube for removal of urine
Receptacle to hold drug
Bulb to force air into receptacle and drug thru tube into bladder

FIG. 1. Instrument for insufflation of drug into bladder

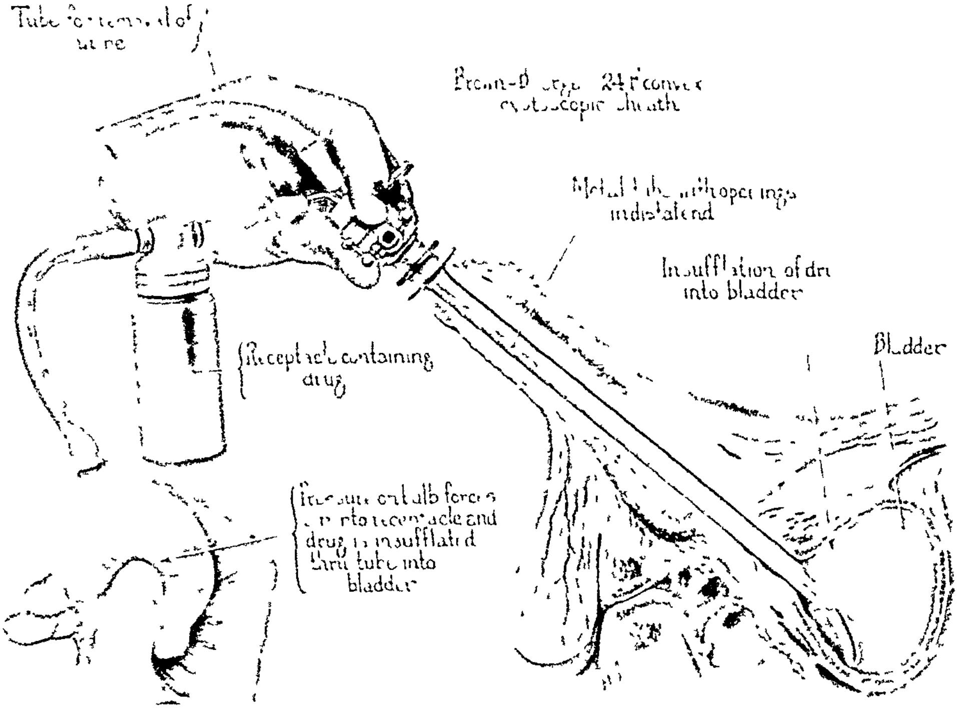
Tube for removal of urine
Brown-Buerger 24 F convex cystoscopic sheath
Metal tube with openings in distal end
Insufflation of drug into bladder
Bladder
Receptacle containing drug
Pressure on bulb forces air into receptacle and drug is insufflated thru tube into bladder

FIG. 2. Using instrument to insufflate drug into bladder

it is best to withdraw the tube and dry by further expressing air through it. Then the atomizer and receptacle are added and the medication blown into the bladder. Most of the air escapes, but moderate distension of the bladder takes place, which facilitates covering the bladder wall.

CLINICAL INDICATIONS AND RESULTS OF TREATMENT IN 11 CASES

The class of patients whom this device was designed to treat suffer with chronic painful urination, frequency, pyuria, and burning. The bladder is usually extensively diseased, the mucosa ulcerated, and the capacity diminished by contraction and trabeculation. The objectives of treatment are to lessen pain, burning, and urinary frequency, to gently stretch the bladder, and to lessen the pyuria by cleansing the ulcerations, thus stimulating healing.

Since powdered sulfanilamide had been reported, by M. C. Myerson,[3] to be useful in relieving pain and cleansing the ulcerations of tuberculous laryngitis, it seemed desirable to try it in bladder tuberculosis. Accordingly, 11 patients were treated with insufflations of sulfanilamide into the bladder. The treatments were administered once a week except for a few patients who received them semi-weekly. Where improvement in the symptoms occurred, the intervals were lengthened and the insufflation gradually discontinued as it is our belief that local treatment of tuberculous bladders should be restricted to the minimum possible because of the traumatic damage caused by the passage of the required instruments.

TABLE 1

NUMBER	SEX	AGE	NEPHRECTOMY	CYSTITIS	RESULT
1	F	25	20 years ago	Moderate	Satisfactory
2	F	21	2 years ago	Severe	Satisfactory
3	M	37	5 years ago	Severe	No improvement
4	F	47	5 years ago	Moderate	Transient improvement
5	*F*	*45*	*None*	*Severe*	*Transient improvement*
6	F	39	17 years ago	Moderate	Improved
7	F	37	7 years ago	Severe	Transient improvement
8	F	36	9 years ago	Severe	Improved
9	F	61	None	Moderate	Satisfactory
10	F	40	8 years ago	Moderate	Improved
11	F	61	21 years ago	Moderate	No improvement

Table I contains a report of the 11 patients treated. All were adults, the youngest being 21 years of age and the oldest 61 years. There were 10 females and 1 male. Nine had had nephrectomy for tuberculosis, and of these 2 had bilateral renal lesions. The length of time since the nephrectomy varied from 21 years to 2 years. All of the patients had urinary frequency with bladder pain, some degree of pyuria, and cystitis ranging up to complete involvement of the interior of the bladder with trabeculation and decreased capacity.

The results of treatment were as follows: 3 were satisfactorily relieved of the urinary frequency and bladder pain, and of these 1 also had a decrease of her pyuria and intermittent hematuria; 3 were somewhat improved; 3 were improved after each treatment, but the improvement was transient and the symptoms recurred later; and in 2 there was no perceptible benefit.

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[3] Myerson, Mervin C.: Sulfanilamide spray for pain of tuberculous laryngitis. J. A. M. A., 130: 1014–1015, 1946.

There were no bad effects from the insufflations and no evidence of toxicity from the use of sulfanilamide. Before beginning the treatments, the urine of each patient was tested with the powdered drug for crystal formation, which was noted once. Most of the insufflations were followed by a temporary reaction which persisted for a few hours.

SUMMARY AND CONCLUSIONS

A new instrument for the insufflation of drugs into the urinary bladder is presented.

The treatment of a series of 11 patients with chronic tuberculous cystitis, and the results of treatment, are described.

It is evident that this procedure is not a cure for tuberculous cystitis. However, it has given some relief to a number of patients. It would seem that there is a field for further trial of insufflation. The topical application of other drugs by this method should be considered. The other sulfonamides, such as sulfadiazine and sulfathiazole, are unsuitable as they cake in the instrument. Chronic interstitial cystitis, Hunner's ulcer, and other chronic bladder inflammations, in addition to tuberculous cystitis, suggest a field for further study.

121 E. 61st St., New York, N. Y.

DISCUSSION

Dr. Julius H. Winer (Beverly Hills, Calif.): Dr. Wang has successfully developed a new instrument to add to his contributions toward the treatment of genito-urinary tuberculosis. For many years his energy has been directed at methods of giving relief to patients with tuberculosis of the urinary tract. With this new bladder insufflator, he has been able to present the urologist with another means of alleviating the pain in tuberculous cystitis.

The structure of Dr. Wang's instrument required the introduction of a 24 F. Brown-Buerger convex sheath. On the urological service at Sea View Hospital, particularly with the numerous male patients having severe tuberculous cystitis, the use of routine caudal anesthesia for cystoscopic examinations was preferred to intravenous anesthesia in these tuberculous patients. I believe this could apply in Dr. Wang's procedure.

One of the dangers of overdistension of the tuberculous bladder must be mentioned; viz., a hematogenous miliary dissemination which occasionally follows urethral manipulation.

We are further influenced in the use of the sulfanilamide powder by Dr. Myerson's findings, that only in definite tuberculous ulceration with secondary infection of the larynx or tongue was the pain influenced by sulfonamide insufflation. Healing of the laryngeal tuberculosis was achieved in 25 per cent of Dr. Myerson's cases after eliminating the secondary infection.

However, the relief of pain occurred in a much higher percentage of cases. If we can give similar relief to our patients with tuberculous cystitis, fewer cutaneous ureterostomies will be performed for intractable bladder pain and possibly the amount of contracture of the bladder will diminish.

Since the histopathology of tuberculosis of the tongue, larynx and bladder is similar in its superficial ulcerative characteristics, and since secondary pyogenic infection of ulcerations is present in most instances, this method of therapy promises to be of value.

This new procedure of introducing a concentrated medicated spray into the bladder will undoubtedly have further application in the therapy of other types of superficial granulomatous lesions of th [illegible] where suprapubic drainage is instituted, insufflation [illegible] opening may be performed.

I should like to ask Dr. Wang approximately what quantity of sulfanilamide powder he uses and whether he has done any studies of the blood level of the drug following insufflation.

Dr. Oswald S. Lowsley (New York, N. Y.): I wish to congratulate Dr. Wang on this addition to our armamentarium.

One of the smartest things I have done in my tempestuous career was to ally Dr. Wang, a man experienced in general tuberculosis, with my department many years ago. He had conducted very scientific and accurate experiments on the use of old tuberculin and various other methods, and has been a source of very great benefit to our department.

One thing about this medical man who does no surgery at all is that he is much more anxious to have patients operated upon who have bilateral tuberculosis than any of us surgeons are, and he stimulates us to operate upon patients who have two bad kidneys if one is better than the other and he draws the line much farther than we do. Instead of being a leveling-off influence, he prods us.

This new method of Dr. Wang's is very useful, as you have seen modestly presented. There have been no extravagant claims, but it does add a weapon for the relief of these patients who are very, very sad in many instances.

DR. O. S. FOWLER (Denver, Colo.): Have you gentlemen ever heard of the fellow who was so lucky that when he fell into a very obnoxious place that he came up with the fragrance of roses? Well, that was I.

Many years ago I had an accident in my office in which I too came out very luckily. I had a woman who had suffered intensely with her bladder from a tuberculous right kidney for 7 years. She had been treated by numerous men with the best known methods during this time, and I was simply relieving her somewhat by injecting sterile mineral oil into the bladder, to coat over the ulcers.

In this treatment 95 per cent ethyl alcohol was injected by mistake. The woman screamed from the severe pain. I had never known of alcohol being put into the bladder, but I thought fast and decided that nothing serious could come from it. She was given opiates at once and for the following 3 days, during which time she passed considerable blood.

However, on the ninth day she came to the office asking "for the same treatment" and I said: "Why, Mrs. M.—— are you crazy?"; "No," she said, "I am not crazy, and I want you to know that I have had the only comfort with my bladder that I have had the last seven years."

From that suggestion I worked out a method of treating tuberculous bladders and kidneys with ethyl alcohol. Some may be treated in the office or you can hospitalize them for 2 or 3 days, which is the better plan, some do not require preliminary opiate, but most need rather heavy preceding dosage.

First empty the bladder with a catheter, then inject 15 per cent alcohol and keep it there about 10 minutes; then the same with 30 per cent, 50 per cent, 75 per cent and 95 per cent.

I have had permanent cure of bladder from even one treatment in office though 5 to 10 treatments are advisable.

The method used in the hospital, after heavy opiates, is to use a 2-way catheter in the bladder. The inflow of alcohol under about 10 inches of pressure, with the outflow the same above the pubic bone, thus gives a gentle bathing of the entire bladder wall.

The dilutions are given the same as the office treatment, clamping the outflow after each injection, until we get to the 95 per cent, then let it drip in about 40 drops per minute, the secreting urine thus dilutes the alcohol to approximately 75 per cent which is the desired strength, so thus I assume we get that approximate dilution.

We have had practically a hundred per cent of permanent relief in all cases and I believe we can say permanent cures.

I have also used this same method by constant drip through a No. 4 or 5F ureteral catheter into the renal pelvis in renal tuberculosis; the above mentioned woman would not permit the removal of that kidney, so since she had pyelitis with mixed infection and a moderate hydronephrosis we did a nephropexy with freeing of the upper ureter, which resulted in bacteria-free urine except that tubercle bacilli remained for years in the urine, but she was well enough to obtain life insurance about 4 years later. Apparently this pure tuberculous infection of the kidney did her no damage locally or systemically.

Now why should alcohol supply this apparent certain relief for tuberculosis of any area to which it can be applied, as I have used it in numerous surgical affections (bones, sinuses, pleurisy, etc.), when a dozen methods have been used for a century, even to the injecting pure carbolic acid into the bladder, all of little or no relief? The answer probably is that since the bacillus is supplied with a waxy capsule and lies at a depth these usual drugs cannot reach it, for it has long been known to be a rather delicate organism when his house has been torn down.

Seventy per cent alcohol penetrates human tissue to considerable depth, this has been known a long time, and is well tolerated by the human tissue, and undoubtedly it will dissolve this waxy capsule. I dare say that ether, chloroform or other solvents would do the same but none can be used ad lib in the human tissue, for alcohol is almost non-injurious to the human and lends itself well in numerous diseases and infections.

The treatment in the hospital covers a time period of about 2 to 3 hours, and one treatment is usually sufficient though I have repeated them in about 30 days in several instances.

If any of you are interested in this I will be glad to give you the details of it.

Dr. Stanley Wang (closing): Dr. Winer asked about the amount of sulfanilamide used. I use 5 gr. or 0.32 gm., which is about the amount necessary to powder the bladder wall. Various other quantities have been tried but this seems to be best. It is about all the instrument will insufflate satisfactorily. Dampening occurs during insufflation and the sulfanilamide powder finally blocks the tube.

Dr. Winer also asked about the sulfanilamide blood level. It has not seemed necessary to check the blood level. Using only 5 gr. of the drug, once or twice a week at most, there is little likelihood of overdosage.

Dr. Howard spoke about the use of alcohol. I have had no experience in local application of alcohol in the bladder. I have used other solutions such as dilutions of bichloride, phenol, ether and others. Some years ago one of the treatments was to anesthetize patients and fill the bladder with a strong solution of phenol which often caused the extrusion of a complete cast of the interior of the bladder. The present trend seems to be toward more bland instillations.

However, I have had some patients quite successful with alcohol internally. Scotch and soda are quite well known. I have two men who are rather insistent that Scotch is what cured them, not my medication, and also it was pleasanter to take.

AGENESIA OF THE URINARY BLADDER AND URETHRA

HAZEN L. MILLER

Maldevelopment of the bladder, except for exstrophy and ectopy of the ureter, is extremely rare. This is especially true of congenital absence of the urinary bladder.

Lower, McCrea, and Huber subscribe to this view and the first 2, along with Eisendrath and Rolnick, remark upon its relatively frequent association with other congenital abnormalities. These abnormalities, say the latter observers, are so frequently incompatible with life as to partially account for the rarity of the condition. Conversely, Huber's ninth edition of Piersol's *Human Anatomy* states: "Absence of the bladder is a very rare abnormality, but in more than 1 case has proved to be consistent with prolonged life, the dilated ureters opening into the urethra, having acted as reservoirs for the urine and the muscle fibres at their constricted orifices having taken on sphincteric action and prevented urinary incontinence."

Lower in Cabot's *Modern Urology* mentioned in 1918 the 6 cases reported in Gould and Pyle's *Anomalies and Curiosities of Medicine* and adds 1 other reported by Winter in 1889. Hinman stated in 1935 in his *Principles and Practice of Urology:* "Vesical agenesis is not so rare but that Estor and Vialleton were able to collect 9 instances. The ureters open externally or into the urethra. The differentiation of marked hypoplasia from a secondarily contracted bladder may be difficult."

I have been able to find only 2 cases of vesical agenesia in the *Quarterly Cumulative Index Medicus* over the past 15 years, both reported in 1939. In the first, that of Eneren, the ureters opened into the posterior urethra. The second case was reported by C. Lepoutre as congenital absence of the bladder with persistence of the cloaca.

The following case is, I believe, an instance of vesical agenesia accompanying spina bifida.

CASE REPORT

A. Z., first seen by me in March 1943, was a 27 year old single white female. She had been admitted to the hospital 3 days previously because of burning pain in her lower abdomen and a dull pain in the right side of her abdomen. A meningocele over the sacrum had been excised at the age of 11 days and bilateral club feet were surgically corrected when 1 year old.

She had always had complete urinary incontinence, for which she wore pads. Incontinence of feces occurred readily if she took a laxative. Catamenia commenced at 11 years and was normal. The abdominal pain had been recurrent for 5 or 6 years in the lower abdomen and for the past 2½ years in the right side. Attacks usually lasted 2 or 3 days but the last attack had continued for 1 month. The family history was negative. No other anomalies were known to have occurred.

The patient assumed in preference for comfort a position of extreme flexion of the thighs. Her height was 4 feet, 11 inches and her weight 110 pounds. The blood pressure was 116/68. The head, neck and thorax were essentially negative except for a hydrocephalic forehead and a rapid pulse rate (120) with the apex 8 cm. to the left of the midsternal line.

The abdomen was soft except for a moderate muscular rigidity in the tender right side where a ballottable mass could be felt. There was also tenderness but no dullness to percussion suprapubically.

In the back a left thoracic scoliosis was evident, and there was a large, irregular scar in the midline over the sacrum and chronic ulcerative dermatitis over the buttocks. The anal sphincter possessed but poor tone which I believe is evident in the photograph (fig. 1).

Except for diminished Achilles, the reflexes were normal in the extremities. A bilateral equinovarus deformity was present and there were surgical scars of both plantar surfaces which were anesthetic to pain, temperature and touch. The anesthetic area extended to well above the malleoli.

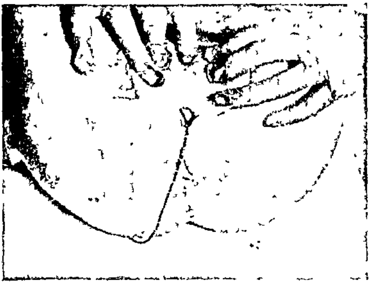

FIG. 1. Showing absence of urethra and adjacent structures. Ureteral catheter (6 F.) is in orifice in anterior vaginal wall and up right ureter to distance of 11 cm.

The appearance of the genitalia is illustrated in figure 1. Urine constantly escaped from between the thickened, edematous and erythematous labia of the vulva hians. Over the entire genito-crural region were numerous patches of excoriation and ulceration.

No urethral meatus was evident, and it was for this reason that I was called upon to see the patient. A nurse and an intern had attempted to obtain a catheter specimen of urine without success.

No structures could be felt between the mucous membrane of the anterior portion of the vaginal vestibule and the symphysis pubis. By means of a vaginal speculum, one source of the flow of urine was shown to be a small orifice on the anterior vaginal wall about 2 cm. from the lower border of the symphysis pubis and slightly to the right of the midline. Urine seeped intermittently from this and the surrounding mucosa was thickened and leukoplakic. A 10 F. soft rubber catheter entered a distance of less than 1 cm. A small cervix was seen in the vaginal vault in its normal position and no urine was observed to escape from the os.

The examination was continued in the cystoscopic room, but no use for a cystoscope could be found. A 6 F. olivary-tipped ureteral catheter was introduced 11 cm. without obstruction. It was impossible to advance it farther. In contrast to the rather clear urine from the vaginal orifice, a thick creamy fluid was aspirated from the catheter. It was not clear whether the catheter was in the bladder or ureter, a 10 per cent sodium iodide solution was instilled slowly and with gentle pressure to find out by means of x-ray. When about 50 cc had been instilled, colicky spasms occurred in the right side of the abdomen and small amounts of the solution returned around the catheter. An x-ray showed the catheter to be in the right ureter and demonstrated a severe degree of hydroureter and hydronephrosis (fig. 2, *A*). The lumbosacral spina bifida is also evident.

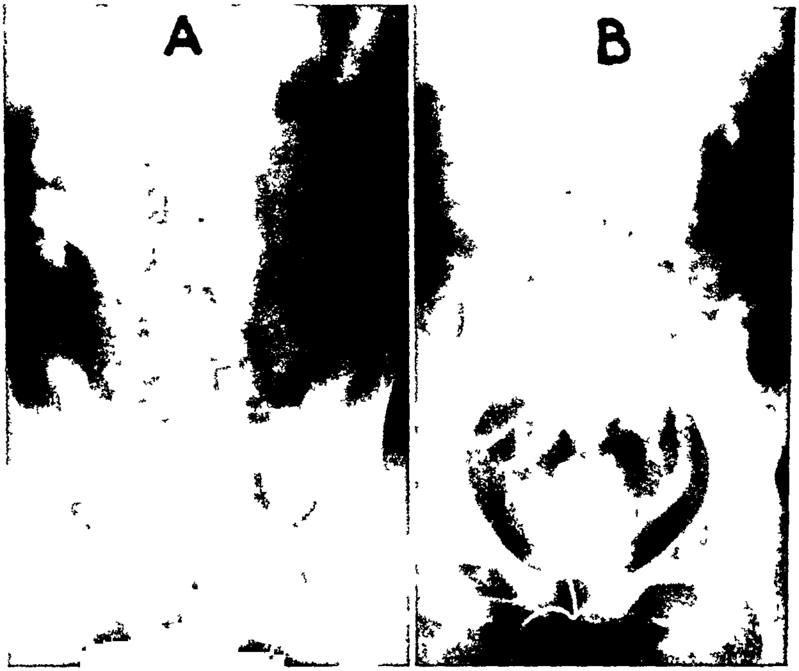

FIG 2. *A*, Retrograde right pyelogram made by instilling 10 per cent sodium iodide solution (50 cc) into ureteral catheter *B*, Excretory urogram made at end of 15 minutes showing left ureter extending to catheter in urinary orifice in anterior vaginal wall

Exploration of the vaginal mucosa failed to reveal a left ureteral orifice. Indigo carmine injected intravenously did not appear in sufficient quantity for identification from either the vagina or the ureteral catheter. A search 2 days later also failed to show more than 1 orifice and indigo carmine appeared only in a faint trace.

The presence of a left kidney and ureter was demonstrated by means of excretory urography, urograms being taken at 5, 15, and 30 minutes. The second of these (fig. 2, *B*) indicated that the left kidney functioned better than the right with less atony of the pelvis and ureter. I believe the shadow of diodrast in the left ureter can be traced to the catheter which was in the orifice of the right ureter.

It is my impression that these 2 ureters meet and drain at a common point, which is in the anterior vaginal wall. While some diffuse shadow of the diodrast and sodium iodide may be seen in this region, it certainly is not circumscribed, as with a bladder, but is probably spillage in the vaginal vault

Culture of the urine from the right kidney yielded E coli Abundant pus cells were present The blood nonprotein nitrogen was 48 mg per 100 cc and the blood Kahn was negative The hemoglobin was 70 per cent, red blood cell count 3,800,000 and leucocytes 11,000

Following catheterization of the right ureter, there was increased pain in the suprapubic region and a rise in temperature to 101 degrees for 2 days This rise in temperature and the rapid pulse then subsided to normal and the patient became entirely free of pain She left the hospital after 10 days in good condition She was advised to consider the benefits to be derived from a bilateral cutaneous ureterostomy, which in view of the atonic anal sphincter seemed the only solution for the urinary incontinence

She was so well satisfied with her condition that she allowed the incontinence to persist She was free of symptoms until August 1946 when she was readmitted to the hospital

Her chief complaint was severe dull pain in the left flank, of sudden onset 5 days before There had also been right abdominal pain of less intensity of 4 days' duration Three days before admission she had vomited 3 or 4 times and on admission the temperature was 101 6 degrees The blood pressure was 142/100 There was extreme tenderness in the right side of the abdomen and in the right costovertebral angle, less on the left The genital and gluteal excoriations were still present

The erythrocyte count was 3,890,000 and the leucocyte count 8,200 The hemoglobin was 78 per cent The blood Kahn was negative and the blood nonprotein nitrogen 38 mg per 100 cc

Discussion of the case with the patient's physician resulted in a decision to evaluate her present renal status by means of ureteral catheterization and excretory urography I had also in mind another maneuver to obtain retrograde filling of the left ureter by means of direct pressure at the urinary outlet in the vagina

Repeated attempts were made to find 2 ureteral orifices A catheter was passed into the cervical os, but no urine was obtained and on x-ray this catheter was found to have coiled into a horizontal figure of 8, apparently in the uterine cavity

Urine emitted in rhythmic spurts from the orifice previously seen in the anterior vagina A 6 F ureteral catheter was passed into this to a distance of 30 cm Cloudy urine flowed from this catheter and a specimen obtained for culture showed Proteus ammoniae An x-ray film showed this catheter to be coiled in a tight circle about 4 cm in diameter a little to the left of the midline suprapubically

Skiodan 20 per cent filled neither ureter nor any cavity which could be interpreted as a rudimentary urinary bladder I made several attempts to force skiodan into the urinary orifice by means of a Van Buren female urethral syringe but could obtain no retrograde urograms upon x-ray examination

Excretory urograms showed pockets of the opaque solution in the calyces bilaterally. The film showed again bilateral hydronephrosis, but not so extensive on the right side as it was 3 years previously.

Before the report of the urine culture was obtained, penicillin 60,000 units and then 30,000 units intramuscularly every 3 hours was commenced tentatively. Such good results were obtained symptomatically that in spite of the report of an insusceptible organism, treatment was continued for 5 days, during which the patient was relieved of severe abdominal pain and backache. She left the hospital August 24, 1946.

On October 7, 1947 the patient was readmitted because of severe bilateral lumboiliac pain, fever, emesis and headache, which had become increasingly severe for the past 2 weeks. There was evidence of toxemia, and tenderness in both flanks and lumbar areas with rigidity of the right side of the abdomen. In the right lumboiliac region there was a scar of an operation performed in May 1947, during my absence, for drainage of a renal abscess.

The temperatúre was 102°, respiration 22, pulse 120°. The blood pressure was 140/100. The blood count showed 2,060,000 red blood cells, 15,000 white blood cells, hemoglobin 39 per cent. The blood nonprotein nitrogen was 59 mg. Extensive gluteal ulcers were still present.

The patient was treated with sulfadiazine 0.5 gm. orally 4 times daily, and penicillin 100,000 units intramuscularly every 3 hours. Intravenous fluids: glucose 5 per cent solution, amigen, and whole blood were administered.

The temperature on October 10 was normal, and the pain less. On cystoscopy, for the first time both ureteral orifices were seen within a shallow recess in the mucosa of the anterior vaginal wall about 5 mm. in diameter. Not more than 2 mm. separated the orifices and the surrounding area appeared fibrotic. There was no perceptible flow of urine. Whistle-tipped 6 F. ureteral catheters were passed, on the right side to a distance of 18 cm.; on the left, 22 cm. No urine was obtained on the right but only pus and blood in shreds upon aspiration. On the left there was a slow, occasional flow of hazy amber urine, which on analysis showed albumin and 20–26 white blood cells per high power field. No growth was obtained in the culture.

An x-ray on October 8 suggested bilateral perinephritic abscesses. Films made 2 days later after retrograde instillation of skiodan 20% showed a large hydronephrosis on the right side and coiling of the catheter inserted in the left orifice in the same manner as encountered on the previous examination in August 1946. However, I believe a reflux of the opaque solution can be detected in the left ureter (fig. 3, *A*).

The patient's condition remained precarious for several days. On October 13, the nonprotein nitrogen was 102 mg. and CO_2 combining power 55 vols. per cent, blood calcium 9.5 mg. and blood phosphorus 5.2 mg. Two blood transfusions were given. On October 17, after the blood picture had improved, I did a left cutaneous ureterostomy. A No. 24 F whistle-tip soft rubber catheter was placed in the dilated atonic ureter, permitting a good flow of cloudy urine which later at times became clear.

The blood nonprotein nitrogen on October 20, was 61 mg and on October 23, 49 mg

On October 20, an abscess above the old right lumbar scar was opened and drained of about 100 cc of thick pus from which E coli was cultured

By November 1 the patient was up in a chair Her blood nonprotein nitrogen was 43 5 mg The blood count showed 3,420,000 red blood cells, 22,600 white blood cells with 57 per cent neutrophiles (55 per cent filaments) 32 per cent lymphocytes and 7 per cent mononuclears The hemoglobin was 72 per cent The urine from the catheter in the left ureter showed 2 plus albumin, many white blood cells and 2 or 3 red blood cells per high power field

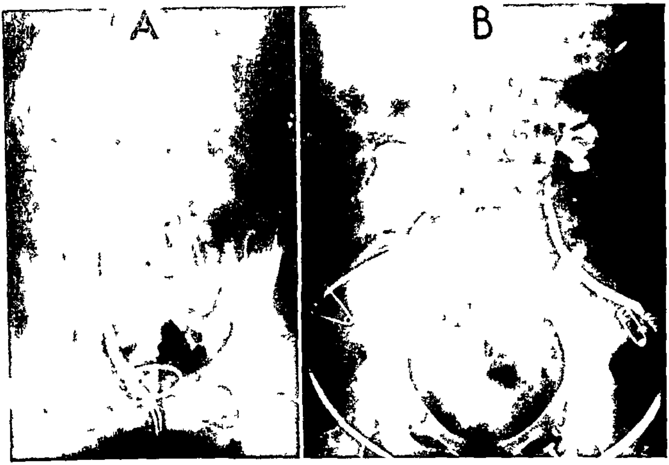

Fig 3 A, Showing position of catheters which have been passed into the 2 orifices in the anterior vaginal wall *B* Retrograde pyelograms after instillation of skiodan solution 20 per cent into soft rubber catheters in ureters Right catheter is 14 F , left 22 F

On November 4 a right cutaneous ureterostomy was done In contrast to the free flexible left ureter, a rigid, fixed right ureter resulting from inflammation, adhesions and fibrosis made proper placement of the stoma in the skin difficult Although division was obtained a little below the iliac bifurcation, perinephritic scarring fixed the ureter near the kidney and, I fear, resulted in some angulation The stoma as on the left side, I managed to place a little medial to the anterior superior spine of the ilium Each ureterostomy consumed about 1½ hours An attempt was made to palpate pelvic structures but little or no additional information was obtained

The temperature rose daily to 102° until the third day, when the right lumbar abscess was drained After this her course was practically afebrile, although there was intermittent abscess formation in the right lumbar region repeatedly opening through the same sinus. This often drains urine even when the ureterostomy tube is in place suggesting angulation of ureter above.

Because of severe nausea and vomiting the sulfadiazine was discontinued on the day after the patient's admission, but penicillin 100,000 units intramuscularly every 3 hours was continued for 10 more days and then 50,000 units following the first operation for 10 more days at which time it was stopped because of a pruritic dermatitis. On and after October 22, the fifth day after the first ureterostomy, the catheters were irrigated daily with a solution of 200,000 units of penicillin in 1000 cc of sterile physiologic saline solution. Penicillin 50,000 units intramuscularly was again started the day after the second (right) ureterostomy, and continued 1 week. Sulfadiazine and sulfamerazine, 0.5 gm. of each were also started postoperatively, but were poorly tolerated and immediately stopped.

The white blood count ranged from 15,000 on admission to 31,000 on October 20, and at the time of her discharge from the hospital was 18,300. The blood nonprotein nitrogen, which rose from 59 mg. to 102 mg. preoperatively, fell to 43.5 mg. after the first operation but gradually rose until on December 16 it was 75 mg. Intravenous indigo carmine on November 25 did not appear in any detectable trace on either side, even with repeated irrigation, and none was observed in the drainage during the day. On November 14, both ureterostomy tubes were injected with 8 to 10 cc skiodan solution 20 per cent with retrograde pyelograms taken (fig. 3, *B*).

The patient was fitted with the Breakey-Burhans type of apparatus for cutaneous ureterostomy drainage, but could not wear it because of postural difficulties and the right lumbar abscesses. Cementing the shields in place and fixing the catheters to them with linen thread have proved fairly satisfactory, but there is an occasional escape of urine around the catheters. Snug fitting of the catheters is hindered by the inelasticity on the right side and the atony on the left.

DISCUSSION

Uterine and vaginal ectopy of the ureter was discussed comprehensively by Hepler. The case here described is one of more than simple ectopy, but rather a complete absence of a bladder and urethra. The tightly coiled catheter (fig. 3, *A*) suggests a rudimentary pouch or contracted bladder. This, however, was entered through the opening of the right ureter well up on the anterior vaginal wall and is more probably dilatation of the lower end of the left ureter. I believe that the 2 ureters enter the vagina at a common point, the left coming in at an abrupt angle.

Proof by surgery or autopsy is lacking, but the findings may scarcely be explained except by assuming absence of a lower urinary tract.

Whether the embryological defect in such case is of the urogenital sinus alone or involves also the allantois is a question which is difficult if not impossible to answer. Failure of development of the urogenital sinus may conceivably lead to atrophy of the unused allantoid portion of the bladder.

This patient's viability with a modicum of health is to me a cause of wonder.

In spite of the marked adynamic stasis she showed remarkable renal recuperation and a competency to combat urinary tract infection.

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A NEW METHOD FOR THE CONSTRUCTION OF A GLANDULAR URETHRA IN HYPOSPADIAS REPAIR

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During the past 20 years specific efforts at curing the glandular, or balanic, variety of hypospadias have been largely abandoned, because of frequent disintegration of the repair, as well as the development of postoperative chordee and strictures involving the glandular portion. Balanic hypospadias has been reported to occur in approximately 1 out of 300 children (Thompson), and except in certain well-selected cases, where definite psychologic factors exist, attempts at its repair have been felt to be unwarranted (Thompson, Lowsley and Kirwin, Creevy).

In the management of the penile, scrotal, and perineal forms of hypospadias as well, the emphasis has been on the attainment of a satisfactory functional, rather than cosmetic, result, insofar as the glans is concerned. Because of the discouraging results which have generally followed attempts to carry the channel beyond the corona, most primary repairs have ended at that point (Cecil). The desirability of submitting the patient to additional operative procedures, in order to accomplish a normal cosmetic result, is certainly highly questionable.

The technique of hypospadias repair, which has enjoyed widest usage at the Brady Urological Institute, is a modification of the Thiersch-Duplay approach. In our hands, it affords a cosmetic result which is far superior to those achieved by other methods; it utilizes hairless skin for the most part; and it can be employed in the most extreme degrees of hypospadias. In the latter varieties, however, fistula formation is not uncommon, and secondary closures are often mandatory. Moreover, as Davis has pointed out, and for reasons to be given below, it is difficult to carry a Thiersch-Duplay repair to the tip of the penis.

The problem in repair of the glans has been to find sufficient tissue to assure proper relaxation of the suture lines. With this in mind, we have devised a simple method, which has sought to augment the amount of skin available for this purpose, by modifying somewhat the first stage procedure of the Thiersch-Duplay operation. This method has utilized to best advantage the essential features of the Thiersch-Duplay technique, and yet has not departed from the basic principles of sound plastic surgery which characterize this technique.

In the past year the results following its use have been so encouraging as to justify a detailed description of the method at this time.

METHOD

The operation is performed in 2 stages, separated by an interval of at least 6 months. The first stage procedure encompasses 1) release of the chordee with excision of all fibrous bands, and 2) preparation of the glans for the second stage operation.

In correction of the chordee, a transverse incision is most often used (fig. 1, *1*). Relief of the ventral curvature is based on the complete removal of fibrous tissue remnants (fig 1, *2*). To aid in lengthening the penis, the hypospadic meatus is often slid proximally.

After the penis has been liberated from its ventral attachments, it is dorsiflexed under moderate tension. A longitudinal midline incision is made on the ventral surface of the glans and deepened until it has attained the summit of the glans

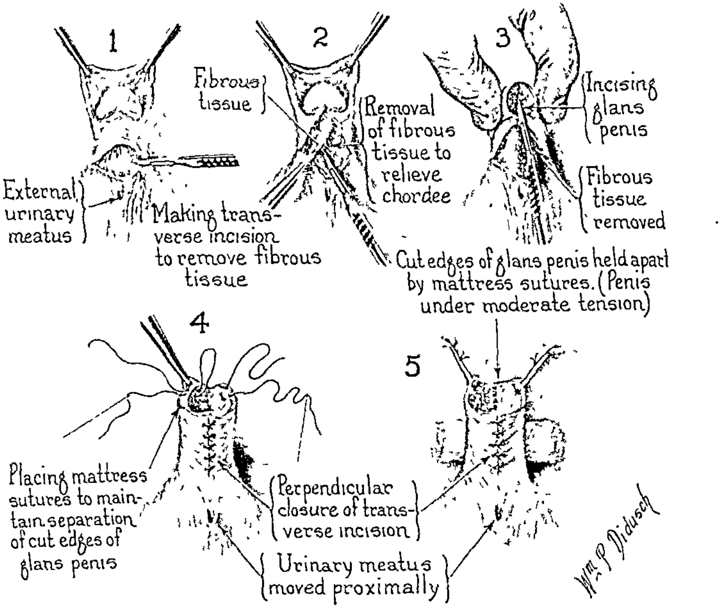
1
2
3
4
5
Fibrous tissue
Removal of fibrous tissue to relieve chordee
Incising glans penis
Fibrous tissue removed
External urinary meatus
Making transverse incision to remove fibrous tissue
Cut edges of glans penis held apart by mattress sutures. (Penis under moderate tension)
Placing mattress sutures to maintain separation of cut edges of glans penis
Perpendicular closure of transverse incision
Urinary meatus moved proximally
Wm. P. Didusch

FIG. 1. Steps in first stage procedure for 1) release of chordee and 2) establishment of *trough on ventral aspect of glans.*

(fig. 1, *3*). The two halves are then spread apart bookwise, and secured to the abdomen by means of mattress sutures of medium silk (fig. 1, *4* and *5*).

Closure is effected by conversion of the transverse incision into a longitudinal one, using interrupted fine nylon sutures.

A snug gauze wrap-around is applied to the penis. The latter is maintained in dorsiflexion by a gauze bolster placed between it and the symphysis (fig. 1, *5*). The bolster also acts to control bleeding from the cut surfaces of the glans, which is generally quite brisk. A dry occlusive dressing is applied.

Diversion of the urine by a bulbar urethrostomy or suprapubic cystostomy is performed only when indicated. Usually, however, an indwelling catheter, introduced through the hypospadic meatus, suffices.

The gauze wrap-around is removed after 4–5 days, and the silk and nylon sutures in 12–14 days. At this time, ample evidence of epithelialization of the urethral furrow is present, and there is no danger of spontaneous union of the halves of the glans.

After an appropriate interval, which is not less than 6 months, the second stage of the operation is undertaken. A well defined gutter is present on the ventral aspect of the glans, which extends to the distal limit and is completely epithelialized. The repair is executed along the classic lines of the Thiersch-Duplay method, with slight modification. The parallel incisions are extended along the borders of the urethral furrow out to the end of the glans. The edges of the tube are approximated by a running subcuticular suture of fine chromic catgut, care being exercised to roll in the epithelial margins. Because of the additional skin which has been induced to line the undersurface of the glans, the suture line in this area is under very little tension, and the caliber of the glandular urethra is in no way compromised. Closure is effected by interrupted fine nylon sutures.

RESULTS

Since the inception of its use 1 year ago, 9 patients have undergone the *first* stage operation, which included the glans-splitting procedure described above. In all of these a wide trough was secured, which extended from the corona to the distal limit of the glans, and by 3 months was completely lined with new epithelium.

Six of the above patients have had second stage repairs, with the urethra carried easily to the tip of the glans at operation. In all but one of these a satisfactory glandular urethra has been achieved, without evidence of local stricture or chordee. In the sixth patient, the sutures approximating the glandular repair were inadvertently removed on the third postoperative day, so that the canal opened widely in this area, and resulted in the establishment of a urinary meatus at the corona.

COMMENT

Since 1925 there have been no descriptions published of new technique specifically designed for the repair of the glandular variety of hypospadias. Constructive operations on the more proximal forms of hypospadias have generally been limited to the establishment of a coronal meatus, although in a few instances attempts have been made to secure a normal glandular urethra (Lowsley and Begg, Humby).

Older methods devised for the successful construction of a glandular urethra may be grouped as follows: 1) Those in which canalization through the substance of the glans was accomplished by a bistoury or special trocar, and followed by the introduction of a graft around a splinting sound or catheter. In some cases, tube grafts were constructed, pedunculated or free, using such varied structures as prepuce (Russell, Young, Mayo), ventral penile skin (Marion), skin from the inner arm or thigh (Nové Josserand), saphenous vein (Legueu), and scrotum (Keyes). Other methods (Bevan, Potel) utilized ventral penile skin flaps, which were drawn into the tunnel, without attempting to construct a tube.

The immediate results of techniques embodying the essential feature of this method, i.e. the establishment of a tunnel through the glans, appeared to be quite favorable. However because of extensive operative trauma to the tissues of the glans, considerable scarring resulted, with contracture of the tunnel, and necessitated frequent urethral dilatations over prolonged periods of time. The use of an inlying catheter for 6 months postoperatively, to preclude the development of a stricture (McIndoe), had its obvious disadvantages, particularly in children. The difficulty in obtaining satisfactory vascularization undoubtedly played a major role in the death of the transplant and subsequent cicatrization, with narrowing of the channel. In a review of tunnelling procedures using pedicle tube grafts derived from scrotal skin, Godard emphasized the great danger of infection as a prime etiological factor. In the Beck-von Hacker approach, the hypospadic meatus was encircled and freed from the underlying corpora, together with a short length of proximal urethra. It was then drawn through a tunnel in the glans and tacked down in its new position. This method was defective, not only because of the liability to stricture, but because it induced varying degrees of chordee.

2) Those in which the Thiersch Duplay type of repair was employed to extend the newly made channel to the tip of the glans (Young). Successful results with this method were infrequent and fortuitous, because of the firm attachment of the glandular integument to the underlying tissues, as distinguished from the abundance of loose skin on the shaft, which was readily available for the construction of a tube. Undesirable tension on the suture line was almost inevitable, and was followed by breakdown of the channel. In those few cases where a satisfactory result was achieved, the urethral groove preoperatively was usually well defined on the ventral aspect of the glans. However, as opposed to the findings in epispadias, the presence of a deep groove on the glans is uncommon in hypospadias, and in fact, the glans frequently may be smooth and convex. Moreover, because of the paucity of tissue available for repair, successfully constructed channels often become strictured, especially at the meatus (Creevy).

3) Those in which a urethral furrow was created by incising the glans, and a pedicle tube graft inserted which had been formed of ventral penile skin (Harvey). Here again, operative trauma to the glans, and difficulty in securing proper vascularization of the graft, predisposed to cicatrization, and militated against a good result. Excessive bleeding increased the tension on the suture lines, and either caused complete wound dehiscence or fistula formation. In Lowsley's 3 stage operation, the glans is partially divided longitudinally in the second stage, prior to bringing the penis down to the newly fashioned scrotal tube. The channel is thus effectively carried to the distal limit of the glans. The use of hair bearing skin, however, has been decried (Creevy) because of the danger of infection arising in the sebaceous glands, and also because of the possibility of calculus formation about a hair nidus (Vermooten).

The success of any plastic procedure on the penis depends on several factors, among which the most important are the acquisition of sufficient tissue to obviate undue stress on the suture lines, the establishment of an adequate blood supply, and the absence of foci of infection. The failure of past methods, which were aimed at the construction of a channel in the glans penis, may be attributed to lack of fulfillment of one or more of these criteria.

The technique which has been described satisfies these criteria more completely than any of the older methods. It provides for a urethra of adequate caliber, with the meatus at its normal location. It also possesses the advantage of requiring no operations beyond those performed for the repair of the more proximal portion of the hypospadias.

SUMMARY

A simple method of hypospadias repair has been described, which allows for the extension of the channel to the distal limit of the glans penis.

The essential feature of this method resides in the establishment of a trough on the ventral aspect of the glans during the first stage operation for release of chordee. With healing, this trough becomes completely epithelialized, thus providing additional skin for the construction of a channel to the tip of the glans. The second stage operation is carried out in the manner of the Thiersch-Duplay technique.

The results of this method have proved most satisfactory. Of 6 patients submitted to the complete procedure, a glandular urethra has been achieved in 5.

Previous methods of repair have been reviewed, and the advantages of the present method cited.

The author wishes to express his appreciation to Dr. William W. Scott and to Dr. Hugh J. Jewett, for their assistance, and to Mr. William P. Didusch for his splendid illustrations.

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CONSTRUCTION OF THE TERMINAL URETHRA IN CORRECTION OF HYPOSPADIAS[1]

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Surgical correction of hypospadias is an easier task for the urologist of today than it was for his predecessors. The sulfonamides and antibiotics now help control the infections which were formerly so often the cause of wound breakdown and failure. The improvement in wound healing has been a tremendous help, but there are still some points of technique which are not entirely satisfactory. We therefore think it worthwhile to mention a variation in surgical technique which, although perhaps not of major importance, has been definitely helpful to us in securing more perfect results.

The ideal result is that which approaches most closely the normal in appearance and function. Some of the older methods of forming the terminal portion of the new urethra give results which by present standards are unsatisfactory. The Ombredanne operation left an irregular and usually gaping urethra which needed later reconstruction and even then did not result in a normal appearing penis.

The other methods of forming the urethra from the skin on the ventral surface of the penis, such as the methods of Duplay and Thiersch, even when entirely successful, left the patient with a urethra that terminated at or behind the coronal sulcus. Often the distal portion of the suture line broke down, leaving the meatus flared and gaping. Whichever of these methods was used, the result was too often a urethra that ended something like a blunderbuss and which did not approximate the normal either in appearance or function.

The tunneling techniques bring the urethra out at the site of the dimple in the glans penis. This is the normal and therefore the most desirable site, but up to the present these methods have had certain disadvantages. Split skin grafts put into the tunnel on a trocar are subject to gradual and protracted shrinking so that it is necessary to keep some sort of a sound or bougie in place for many months to halt the tendency to contract. Free full thickness grafts, so inserted, have less tendency to shrink but do not always "take."

The method which we are about to present is a modified tunneling operation and was discovered accidentally while using a Duplay type of procedure. The penis had been straightened after the method which Nesbit published several years ago. We found that the foreskin flap which had been transplanted to cover the bare area on the ventral surface was so large that there was an excess of skin. This excess would have caused a transverse fold or wrinkle in the new urethra. In trying to decide how best to overcome this difficulty, it occurred to us that the urethral tube could be made long enough without using all the skin available and a tunnel made underneath the excess, thus bringing the newly-formed urethra out at the site of the dimple. On trying this, it worked so very well that we continued to use it, and with consistent success.

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., July 3, 1947.

Our present procedure is to straighten the penis after making a complete encircling incision, as advocated by Nesbit. Then as much of the foreskin as possible is transplanted to the ventral surface by making a button-hole. It is easy to determine just how much can be thus transplanted by stretching the penis to its full length and measuring off the exact amount that will be necessary to cover the dorsum without tension. All the rest is transplanted.

This usually provides considerable excess of skin on the ventral surface. The excess varies from 1 to 5 or more centimeters, depending on the amount of the urethral defect and the length of the foreskin. The amount of excess is measured by stretching the penis to its full length and measuring the amount that will be required to reach from the hypospadic meatus to the dimple on the glans. This is best done only after the tissues have become well healed, soft, and mobile and their blood supply is well established; an interval of several months after the straightening. The excess of skin which remains is measured and this measurement is the length of the tunnel.

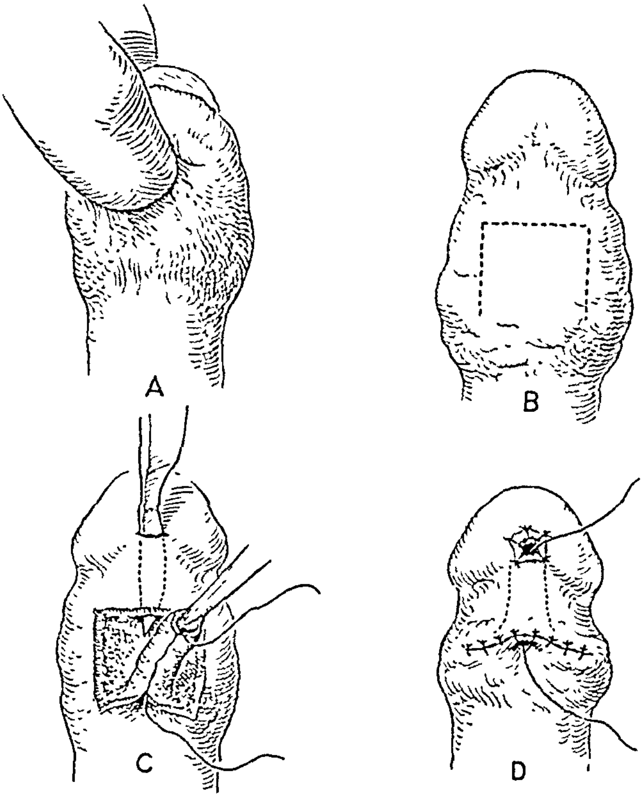

FIG. 1. *A*, Showing how loose skin is pulled distally to measure how much is needed to reach dimple. *B*, Flap outlined. *C*, Flap formed into a tube and tunnel made. *D*, Tube drawn into place and sutured.

A skin flap is constructed (fig. 1). This flap must be the same width in millimeters as the caliber of the desired urethra in numbers of the French scale.

The tunnel is made by incising the dimple, through the tissue of the glands and under the remaining skin (fig. 2, *A* and *B*). Bleeding may be profuse at

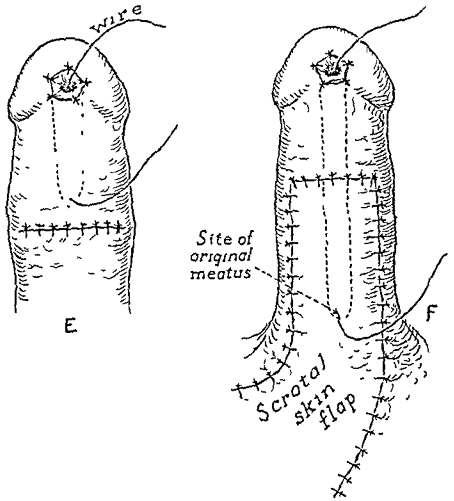

FIG 2 *E*, Showing how a complete procedure may be done at one operation if defect is not great *F*, Where defect is large, method may be combined with Duplay procedure. Only distal portion of new urethra can be brought through a tunnel. Large bare area is covered by a scrotal skin flap.

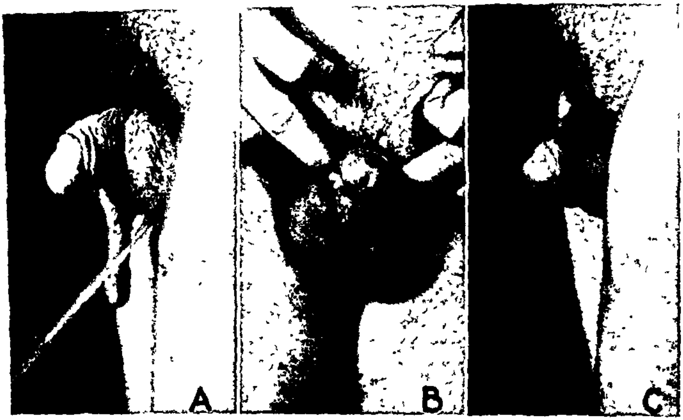

FIG. 3 *A*, A patient, after straightening, showing scrotal pedicle skin flap prepared; meatus between bifid scrotum. *B* and *C*, Final result.

first but is easily controlled by pressure or the use of clotting agents such as thrombin solution. The flap which has been raised is then formed into a tube around a catheter by using a continuous subcuticular stainless steel suture. The tube so formed is then drawn through the tunnel and the edges stitched to the adjacent edges of the glans at the dimple. The edges of the skin flap incision fall together quite naturally and are sutured with interrupted cotton or plastic silk worm gut. The catheter is removed and a pressure dressing is applied. Usually at this time a pedicle flap is raised on the scrotum for use at the final stage.

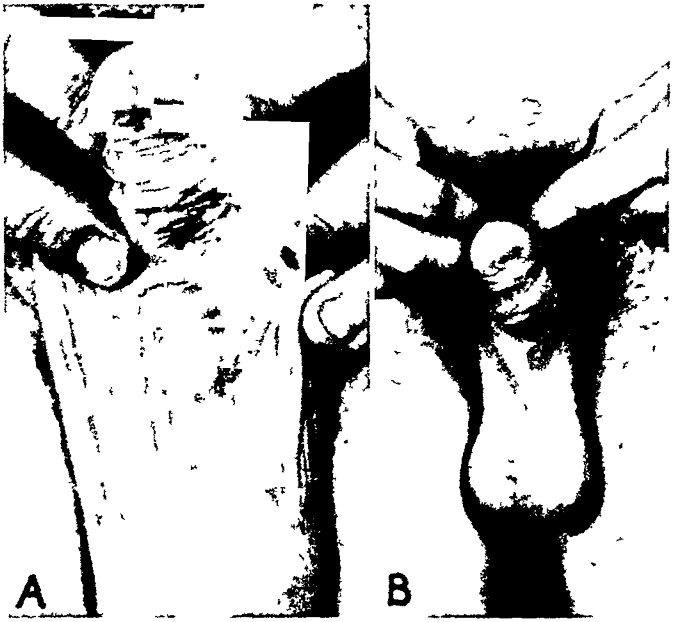

FIG. 4. *A*, After straightening, before urethroplasty; peno-scrotal meatus. *B*, Final result.

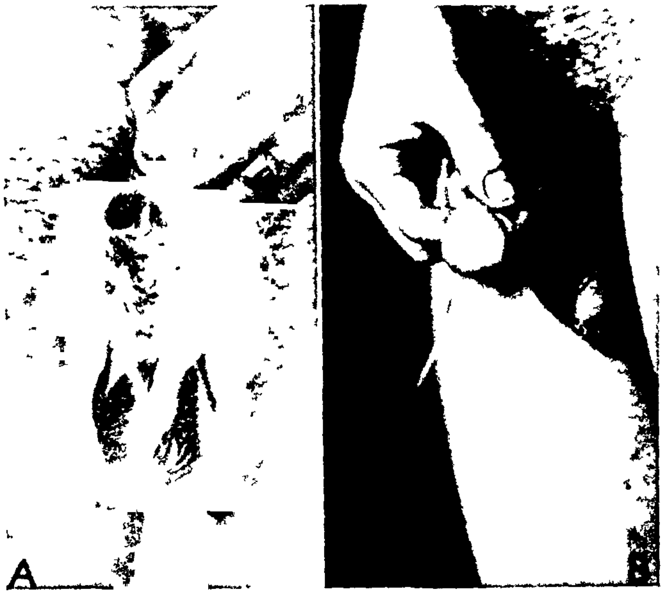

FIG 5. *A* and *B*, Final result in case with meatus about half-way along shaft

When this is healed, the patient has the terminal 2 or more centimeters of his urethra and the intervening segment is constructed at the final operation by the method of Duplay The bare area is covered by a scrotal flap without any tension or superposition of suture lines

If the urethral defect is not too great, it may be possible to reconstruct the entire necessary portion by this method, in which case the remaining skin can be brought down to completely cover the newly-formed urethra without any superposition of suture lines whatever (fig 2, *C* and *D*)

Where the defect is quite large it is possible to combine this technique with the Duplay method of constructing the urethra Thus the entire urethra is formed at 1 stage instead of 2 Up to this point we have used 2 stages

The portion of the urethra so constructed can easily be sounded or dilated when necessary We have found the early tendency to contract to be controlled without difficulty, apparently due to the fact that the skin is full thickness and a marked tendency to shrink is not present See figures 3, 4 and 5

The advantages of the method are that healing of the terminal portion is excellent and breakdown unlikely It gives a normal appearing penis with the meatus in its proper position The patient will never be embarrassed by his condition, since the end result is almost indistinguishable from normal except on close examination The functional result is likewise excellent as the stream is normal and does not spray

SUMMARY

A method is presented by which the terminal portion of the reconstructed urethra is formed from a foreskin flap and brought through a tunnel to the dimple in the glans This results in a very normal appearing and functioning urethra with the meatus normal in size and normally placed

PLASTIC RECONSTRUCTION OF THE PENIS[1]

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Fortunately the loss of the penis is rare. Its occurrence at any time is deplorable but in a young man it is particularly catastrophic psychologically. Aside from its sexual aspect the loss of the phallus incurs a definite handicap when attempting to void in the normal male position. With the nerves intact in the stump and with testicles present, both sensory and hormonal factors remain and titilation of the remnant cavernous bodies can result in a sexual impetus to the extent of pollution and ejaculation. The patient is not necessarily sterile although the modus apparandi for the transmission of sperm through the pendulous urethra is missing.

The repair of this deficiency by plastic reconstruction of the amputated penis can be satisfactorily accomplished. The new organ can assume the normal physiological functions not only of urination but also can afford connubial gratification to both participants during coitus.

A satisfactory reconstruction of the penis was first reported in the German literature by Professor N. A. Bogoras in 1936. After several attempts he successfully restored, by plastic procedure, the major portion of a penis lost in an accident. Restoration was accomplished by utilizing tube skin grafts into which rib cartilage was implanted.

In 1943, A. P. Frumpkin reported "The Reconstruction of the Male Genitalia" which was translated in the *American Review of Soviet Medicine* (February 1944). Following the technique of Bogoras, Frumpkin was able to successfully repair total traumatic amputations of the penis which at times left only remnants of the cavernous bodies ending at the symphysis and even occasionally contracting under it. Frumpkin's work so impressed the American-British-Canadian Commission to the U. S. S. R. in 1943, that they reported his plastic surgery as obviously outstanding in the field of genito-urinary surgery and that results obtained in the reconstruction of external genitalia lost as battle casualties were dramatic.

In many mammals erection of the penis is assisted by the presence of a baculum or os penis. This baculum or "little stick" was observed by Aristotle in the fox, wolf, and martin. It is present in marsupials such as the kangaroo and opossum; in chiroptera such as bats; rodentia such as squirrels, beavers and rabbits. Cetaceans such as dolphins, porpoises and whales also have an os penis. Jaeger states that an os penis often may be almost as long as the phallus, it is often grooved and generally hooked, and may have a knob at one end. It begins its development as a pair of cartilages. This bone may vary in length from a few millimeters in some of the smaller mammals, to 55 cm. in the walrus and 2 meters in the whale.

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., July 3, 1947.

For the reconstruction of the phallus we have utilized the technique of Bogoras and Frumpkin but have modified their hypospadic repair.

SURGICAL TECHNIQUE

The operative technique for the reconstruction of the phallus is carried out in 4 stages and requires a total of about 9 months for its complete accomplishment. Development of the phallic graft and its transplantation is accomplished in 3 stages. The fourth stage is devoted to the correction of the hypospadic pedicle graft.

First stage. The first stage consists of the development of the phallic tube graft from the lateral abdominal wall and the obtaining and implanting of the rib cartilage. An incision about 6 cm. long is made to expose the cartilage of the eighth or ninth rib from the sternum to the costochondral junction (fig. 1). The fascia and muscle layers are incised, exposing the perichondrium which is stripped from the cartilage by means of a periostial elevator. The cartilage is then removed and placed in saline. The perichondrium is approximated and the skin is closed. The tube graft is then developed by making 2 parallel incisions, about 6 or 7 cm. apart, starting from the lateral costal margins at the posterior axillary line and continuing the incisions downward and anteriorly to a point somewhat anterior to the external iliac spine. The incisions are developed through the entire skin layer including the subcutaneous fat down to the deep layer of the superficial fascia. The tissues between the two incisions are undermined, freeing a flap which remains attached at both ends. A tube graft,

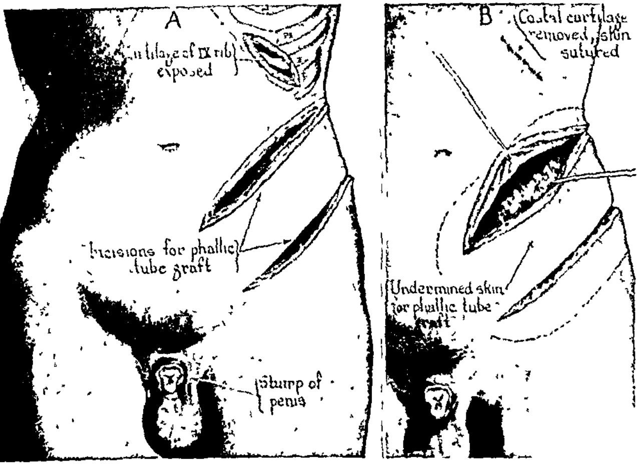
A
Cartilage of IX rib exposed
Incisions for phallic tube graft
Stump of penis
B
Costal cartilage removed, skin sutured
Undermined skin for phallic tube graft

FIG. 1. First stage. A, Site of incisions for phallic tube graft and exposure of rib cartilage. B, Showing incision to remove costal cartilage closed. Undermined skin for phallic tube graft is demonstrated

surrounded by epidermis, is constructed by suturing the cut edges of the middle flap together with interrupted sutures of fine silk. The cartilage, which is slightly curved, is inserted in the cephalad portion of the tube so that the concavity faces upward when grafted to the penile stump. The skin between the 2 incisions is undermined for a sufficient distance to permit the approximation beneath the tube graft. See figures 2 and 3. Tension on the suture line must be minimum.

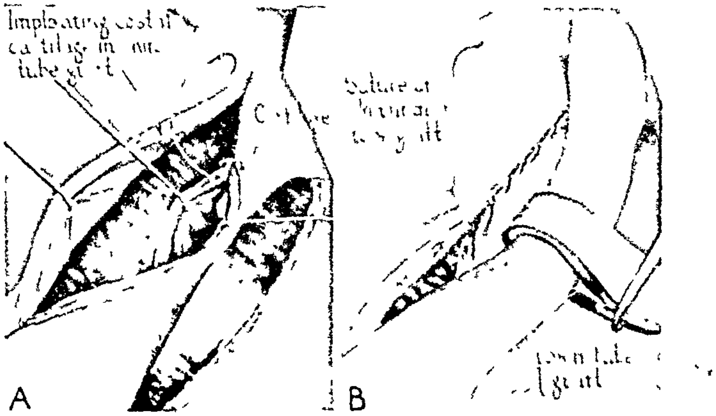

FIG. 2. First stage. A, Implanting rib cartilage in skin tube graft. B, Approximating undermined skin edges beneath pedicle graft.

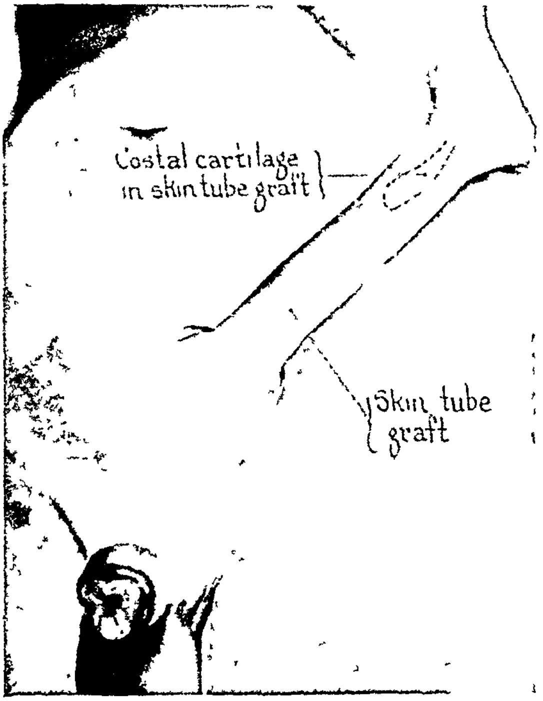

FIG. 3. First stage completed. Showing rib cartilage in place

Second stage. The second stage can be considered about 6 weeks later and consists of diversion of the urinary stream and the transplantation of the tube graft with cartilage to the penile stump. A cystostomy is done (fig. 4, *A*). The attached tube graft containing the embedded cartilage is freed at the cephalad attachment. The cut end of the graft should bleed freely if a successful trans-

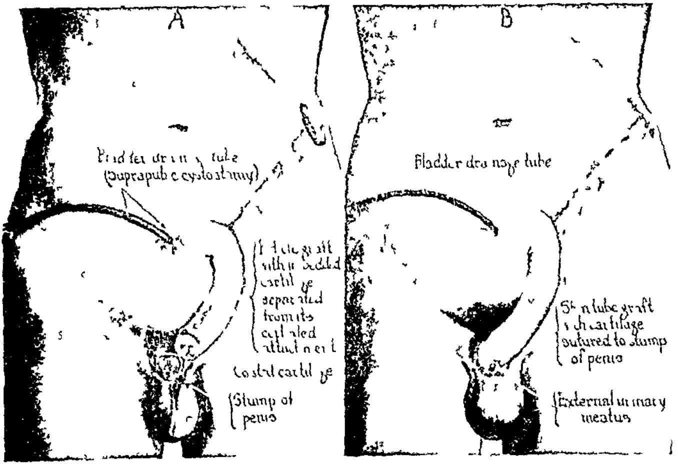
A
B
Rubber urinary tube (suprapubic cystostomy)
Pedicle graft with embedded cartilage separated from its cephalad attachment
Costal cartilage
Stump of penis
Bladder drainage tube
Skin tube graft with cartilage sutured to stump of penis
External urinary meatus

Fig. 4. Second stage. Urinary stream diverted by means of cystostomy. Pedicle graft with embedded cartilage is separated from its cephalad attachment. *B*, Completion of second stage.

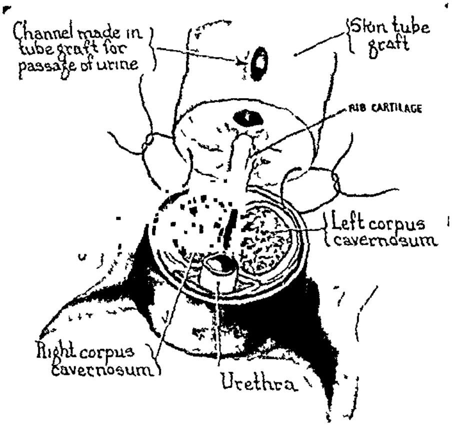

Fig. 5. Second stage. Pocket made in corpora cavernosa for reception of rib cartilage.

plant to the penile stump is to be expected. The cartilage in the tube graft is exposed and freed of its fibrous attachment for about 1 cm. The scar tissue on

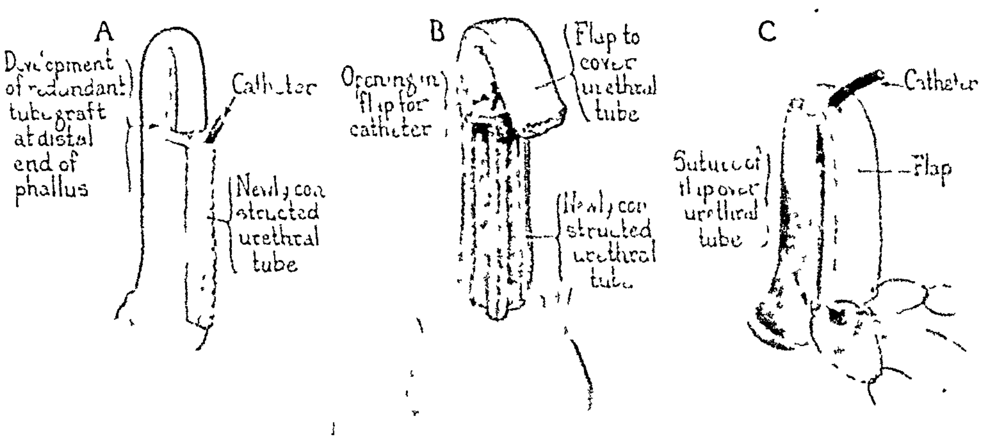
A
Development of redundant tube graft at distal end of phallus
Catheter
Newly constructed urethral tube
B
Opening in flap for catheter
Flap to cover urethral tube
Newly constructed urethral tube
C
Catheter
Flap
Sutures of flap over urethral tube

FIG. 9. Fourth stage. *A*, Redundant tube graft at distal end of phallus is being developed. *B*, Further development of flap to cover ventral defect over newly constructed urethra. *C*, Flap in place.

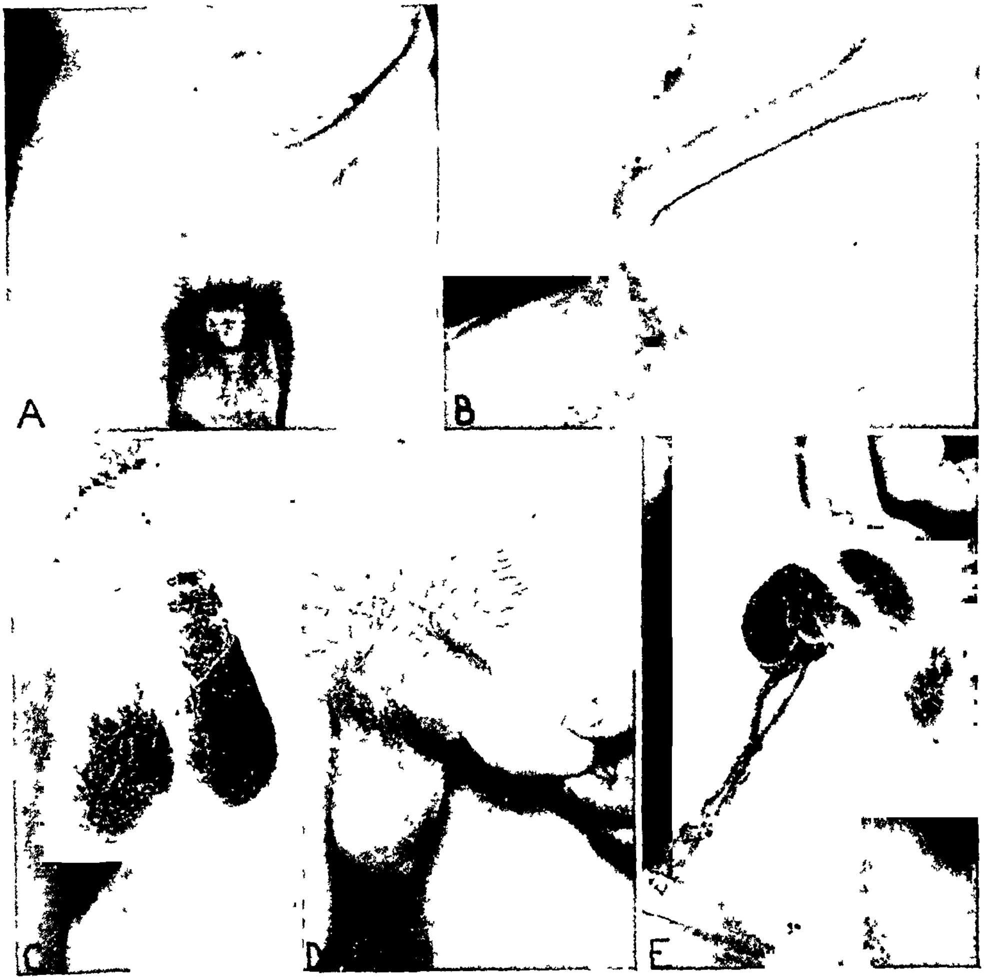

FIG. 10 *A*, iterior view, showing pedicle graft in its first stage. *B*, Lateral view. . penis, anterior view *D*, Reconstructed penis, lateral view. *E*, Patient voiding.

closed with fine silk. See figure 7. The patient at this stage has an acquired hypospadias. The purpose of the fourth stage is to correct this condition. As a means of covering the newly developed pendulous urethra in the fourth stage a graft about 6 cm. in length is developed in the scrotum and left attached at each end. Meticulous care must be exercised to assure absolute hemostasis.

Fourth stage. This final stage may be carried out within 6 weeks following the previous procedure. We have modified a technique described by Goodhope and Wehrbein and suggest a procedure of our own. See figures 8 and 9. Two parallel incisions, 3 cm. apart, are made on the ventral aspect of the shaft of the reconstructed penis through the entire skin extending from the distal end to the urethral stoma. These incisions are undermined, leaving about ½ cm. of the flap attached in the midline, and the free edges are sutured together without tension through the subcuticular layers only, making a tube to form the pendulous urethra. The urethral stoma is freed of its scar tissue and sutured to the newly constructed urethral tube. At this point the entire urethral canal has been formed but a denuded surface remains to be covered. To accomplish this the scrotal pedicle graft previously developed in stage 3 is incised longitudinally throughout its entire length and detached at its distal end. The flap thus formed is brought over the raw surface of the shaft, closing the defect by suturing its edges to those of the skin of the penis with interrupted sutures of fine silk. A bag catheter is then placed through the newly developed urethra into the bladder.

An alternate procedure in the fourth stage, in closing the raw surface on the ventral aspect of the penis, would be to eliminate the use of scrotal tissue and utilize the redundant tissue from the pedicle graft which would ordinarily be amputated. The tube graft of the abdomen should be developed to its maximum length for this purpose.

A transverse incision on the ventral aspect of the newly constructed phallus could readily be made about 2 cm. distal to the tip of the cartilage, the tube graft then split toward its distal end to provide an adequate flap of viable tissue to cover the ventral defect completely. A slit in the portion of flap covering the new urethral orifice would be made to permit the newly formed urethra to be brought out and sutured to its proper position.

Following the removal of the urethral catheter after 8 to 12 days, the suprapubic tube is clamped off and is then removed when the patient is urinating through the urethra satisfactorily.

The photographs (fig. 10) demonstrate an amputated penis in a young married man 26 years of age. The length of the penile stump to the symphysis pubis was about 2 cm. The results obtained from the plastic reconstruction are to be seen in the 3 following photographs.

Functionally the patient can now urinate normally. Sexual gratification is apparently satisfactory to both his wife and himself. Coitus was permitted 4 months following completion of the last stage.

Pain and touch sensation were found to develop to the distal end of the reconstructed organ. The sensation of touch appeared to return first showing a definitely advancing zone of sensation while pain and temperature returned more slowly and required about four months before the entire shaft was sensitive.

SUMMARY

The primary purpose of the plastic reconstruction of the penis is to enable a patient with an amputated penis to urinate normally without soiling himself. Sexual function may also be successfully restored.

The literature is reviewed and a technique for the reconstruction of a penis capable of its normal function, utilizing a skin tube graft from the abdomen and cartilage from the rib, is presented.

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DISCUSSION

Dr. Donald A. Charnock (Los Angeles, Calif.): The procedure which Dr. Kiefer has outlined to us consists of the construction of a pedicle graft which he inserts beneath the skin and through the glans. We know from experience that pedicle grafts constructed from the transplanted foreskin maintain their calibre and readily adapt themselves to their new site. They do, however, show a tendency towards contraction in length. I believe that the method by which Dr. Kiefer handles the pedicle graft might have a tendency to aggravate the curvature of the shaft. When we remember that the graft itself at times contracts in length, this might result in an increase of the ventral curvature.

My experience with placing the urethra through glandular tissue has not been so satisfactory as that which Dr. Kiefer reports. We have found that the tendency to stricture is so great that dilatations have been necessary over an extended period. For this reason we are content to construct the urethra only to the level of the corona. This gives a servicable penis without stricture. We believe this outweighs the cosmetic results obtained from inserting the urethral tube through the glans.

The proof of any operation is the results obtained. Dr. Kiefer's success is to be commended.

The problems of hypospadias will not be solved by any one type of procedure. It is my feeling that successful operations depend upon a carefully planned technique and close attention to proven surgical rules. The correction of hypospadias must meet two criteria: the shaft must be relatively straight, and the urethra must be of adequate calibre. The success of these operations requires gentle handling of the tissue, meticulous approximation of skin flaps without tension and freedom from infection and hematoma. We have derived much help from the plastic surgeons. They have taught us the appreciation and use of small nontraumatizing instruments. They have stressed the construction of skin flaps with adequate blood supply. They have proven that simple, carefully planned steps are more successful than elaborate procedures. If we apply these basic lessons; this most exasperating of operations will eventually be solved.

Dr. David M. Davis (Philadelphia, Pa.): I am delighted to hear that Dr. Kiefer is interested in bringing the meatus to the tip of the penis where it belongs, to give a proper and normal looking result. I personally have had a similar interest for a good many years, and I am glad to see that I now have someone to support me in that direction.

About 7 years ago there was published in *Surgery, Gynecology and Obstetrics* an article written by myself, in which the technique was described of creating tube grafts of preputial skin immediately in its original position and not first transplanting it to the ventrum of the penis. This simplifies the procedure a great deal, and in many cases permits a tube graft as much as 5 cm. long to be made with an excellent blood supply, since it is attached at its proximal end. It is then brought through a tunnel in the glans and as far down the penis as the length of graft will allow, so that often practically no Thiersch-Duplay repair is necessary.

I shall not take any more of your time, but I have a few slides to show some results of this method which I feel I can recommend highly without reservation.

(Slide) The first slide that I have put in shows the results of an Ombredanne operation performed by another surgeon. This is merely for contrast. This patient came to us in order to have this lamentable situation corrected, and it is now being corrected.

(Slide) Each slide shows the end result of a separate case. These are all penoscrotal hypospadias, and there are 8 of them.

I should like to show 2 more cases of perineal hypospadias. (Slide) The first is an extraordinary case in which the urethral orifice is about 1 cm. anterior to the anus; the penis lying subcutaneously, as you can see. This was done in 2 stages.

(Slide) This shows the situation after the first stage. The penis was freed and turned up on the abdomen and the hairless skin prepared for the construction of the new urethra. The old urethral orifice is plainly visible. (Slide) This is the end result.

(Slide) This is the other case of perineal hypospadias. You can see the scar running well down the perineum, almost to the anus. There was present a vagina, about 2½ cm. long. The vagina was excised, the urethra constructed, mostly in the Thiersch-Duplay method, and with a tube graft for the glandular part. You can see the end of the tube graft which had been brought through the tunnel in the glans. The next slide (slide) shows the function obtained.

Dr. H. L. Wehrbein (Brooklyn, N. Y.): We all have removed a phallus, but we never have made one. In cases of carcinoma of the penis in fairly young men it has occurred to me that some plastic reconstruction should be undertaken, but I have not seen one case in young men when the disease was not fatal.

Aside from these amputation cases, I have seen only 2 patients in whom the amputation was not performed in the surgery. Both were fairly young Negroes. One lost about 40 per cent of his phallus when an irate husband found him in flagrante delicto, tried to kill him with a machete and missed. The other one had lost only 25 per cent, having been punished by his wife for infidelity. Both these men came in because of the stricture which had developed at the new meatus; both refused reconstruction operations and stated that their sexual activities were satisfactory, which shows that the psyche plays a very minor role in some people.

Explosives, bullets, etc. may destroy the penis, but I have not seen any such cases. Industrial accidents occasionally damage the phallus; as a rule, denudation takes place and not amputation. We have repaired several of these, but they were easy jobs in comparison to the one under discussion.

It is apparent from the illustrations that a good job has been done. I have no fault to find with either the planning or the execution of the operations. We have used the so-called double pedicle bridge grafts with excellent results in plastic operations for the correction of hypospadias deformities. However, we always prepare the tube for transplantation by tying off intermittently the pedicle which is to be cut.

It is noteworthy that the first tube made in this case is used as a cylinder and is not unfolded as we always do. Therefore, its diameter is of great importance. A width of 7 cm. will result in a tube about 2 cm. thick—allowing for some shrinkage—and that cannot be changed.

The author's suggestion to make a skin tube long enough to replace the penile deficiency and to cover the new distal urethra does not appeal to me. I do not know how long a bridge graft can be and still be safe for transplantation, but I would guess that 15 cm. is the limit. This would barely be enough in cases of great loss.

The use of a urethral catheter during the fourth stage is not necessary. It can be used as a mold while sewing the urethra, but to leave it in place invites infection.

The remarkable return of touch sensation in transplanted skin is quite astonishing and has been noted by us many times. However, it is hard for me to believe that in this case it has much bearing on the patient's ability to achieve orgasm. I would rather assume that the stumps of the corpora cavernosa transfer the necessary stimuli.

Dr. O. A. Nelson (Seattle, Wash.): Dr. Bergman has shown us some excellent work in reconstructive surgery of the male phallus. There are two good silent teachers in urologic surgery. One is the use of local and regional anesthesia and the other is plastic and reconstructive surgery. No one can do much of this type of surgery without learning the importance of gentle handling of the tissue, of the blood supply and the elusive shrinkage of tissue. At the time of the operation, the surgeon must be able to visualize what is to be the appearance of the finished product. The question has often been raised whether such an extensive procedure is justifiable. That will depend, of course, on the individual patient. In this instance Dr. Bergman has answered the question definitely in the affirmative. His patient is, no doubt, extremely grateful. The mental depression and torture that some of these patients suffer are not fully realized by many of us. Dr. Bergman has accomplished a difficult feat in reconstructive surgery.

Dr. Ralph H. Jenkins (New Haven, Conn.): During World War II, quite a number of boys were sent to the hospital for operation of first degree hypospadias, because they were rejected for service in the Navy. These boys were perfectly normal otherwise. It so happened that the Surgeon General was an old classmate of mine, and I wrote to him, and told him I could see no reason why a boy, otherwise normal, who had first degree hypospadias was not physically fit for Naval Service. After much correspondence he agreed that first degree hypospadias was not a cause for rejection.

Looking at Dr. Kiefer's slides, it appeared to me that he was correcting cases of first degree hypospadias.

I find that many doctors spend more time, when operating upon hypospadias, trying to build up the urethra than correcting the chordee. The patient, upon getting married, is pretty unhappy when he finds the chordee has not been corrected properly.

My suggestion would be that more time be spent in correcting the chordee, because the patient can much more easily tolerate sitting down to urinate, than being unable to carry out his marital functions.

Dr. Joseph H. Kiefer (Chicago, Ill.): I think, Dr. Jenkins, you must have misunderstood. All of these patients had straightening of the curvature as the first surgical procedure, before the operation described was done.

I agree with you that it is more important that the penis be straight than that the urethra come out at the end. Half the population (the female half) urinates sitting down. So one can live and be perfectly comfortable urinating sitting down. It is not essential to health; or at least to physical health that a man be able to stand up and void.

But there are psychic factors to think about. They are not important in the child. Parents often bring their children and want the correction done at the age of 3 or 4. They are afraid the child will get ideas of inferiority while he is in school. I have not found that to be true. They do not start to develop self-consciousness in this respect until after puberty. So you have until that time.

Men do not like to have any deformity. They like to be able to stand up and urinate with the rest, without any one noticing anything out of the way. To themselves, I think they like to feel that they are not incompletely developed; that they are as near normal as the rest of the men. I think we all would like to feel that way. So there is a definite reason for trying to get an end result that is as normal as possible.

Dr. Charnock commented about narrowing when you tunnel through the glans. It is true that they do develop some constriction, but so far it has not been severe, and after a period the tendency has seemed to diminish. I agree with Dr. Charnock as to the necessity for meticulous attention to detail and gentle handling of tissues as essential to success in this type of work.

NEUROFIBROMA OF TUNICA ALBUGINEA TESTIS

BENJAMIN LEVANT AND MILTON A. CHETLIN

From the Department of Urology, Montefiore Hospital, Pittsburgh, Pa.

Tumors of the testicular tunics are indeed rare. Hinman and Gibson (1924) in a review of the literature of testicular tumors collected 4 authentic cases of the tunica albuginea, all benign fibromas. Thompson (1936), reviewing the literature, reported the same 4 cases. Silverton and Welsh (1937) reported another tumor of the tunica albuginea, also a fibroma. Malignant tumors of the tunica albuginea have never been reported. The following is a case report of neurofibroma of the tunica albuginea testis that recently came under observation.

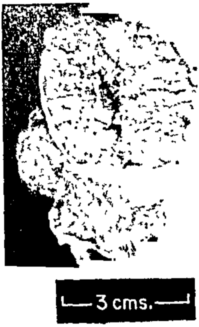

FIG. 1. Testicle and tumor removed at operation

CASE REPORT

W. M. F., 59 years of age, was admitted to Montefiore Hospital, December 23, 1946. His family history was negative. He gave a history of syphilis 20 years ago and gonorrhea 4 years ago. The patient stated that he had been aware of a nodule in the right testicle for about 6 months. It had steadily and painlessly increased in size. There was no history of trauma.

No masses were palpable in the abdomen. Both external abdominal rings were small, and there was no inguinal hernia on either side. The prostate was soft and boggy and slightly enlarged. The left testicle was of normal size and consistency. The right testicle revealed a hard, nodular swelling about the size of a hazelnut near its base. The epididymis was well-outlined and normal to palpation. Wassermann was negative; blood pressure 140/70. Blood count: Erythrocytes 4,200,000, leucocytes 4,600, polymorphonuclear neutrophiles 54 per cent, lymphocytes 46 per cent, hemoglobin 87 per cent. Urine: specific gravity 1.024, acid, albumin and sugar negative, occasional pus cell, no casts. The diagnosis was malignant tumor of the testicle, and immediate operation was advised.

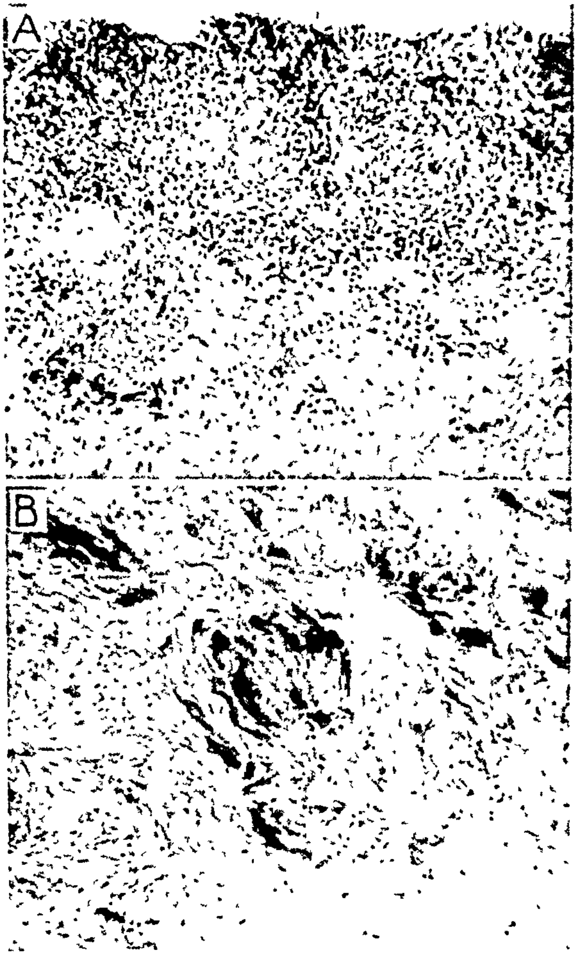

FIG. 2. *A*, Photomicrograph of tumor of tunica albuginea testis, showing concentric layers of fibroblasts, whorl formation and pseudo-palisades. H and E stain. *B*, Photomicrograph of tumor, using a Wratten B filter on panotomic film to show strands of nerve fibers and sheaths, which appear black here. In natural color these fibers take a salmon-red stain. Masson trichrome stain.

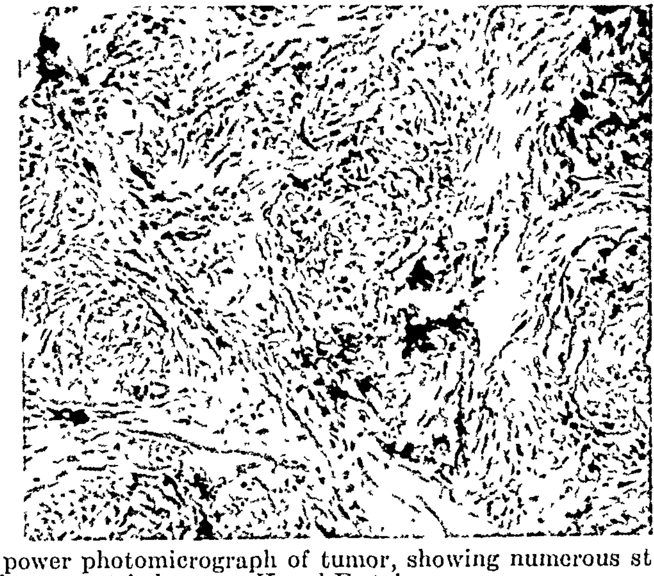

FIG. 3. High power photomicrograph of tumor, showing numerous strands of collagen tissue arranged in concentric layers. H and E stain.

A right epididymo orchiectomy was performed under spinal anesthesia A right scrotal incision was made The cord and vas deferens were ligated with chromic catgut and divided The testicle was then easily removed and the skin sutured with interrupted silk sutures On sectioning the resected testicle, a very hard white tumor of tunica albuginea testis was found (fig 1)

Pathologic report (Dr K Y Yardumian) "Specimen consists of a testicle with its epididymis, tunica, and part of the spermatic cord On the lower pole of the tunica albuginea testis there is a hard mass, oval in shape, and well encapsulated It measures 1 by 0 5 by 0 3 cm On sectioning, it is pearly gray in color, solid throughout, and firm, almost cartilaginous in consistency The tumor apparently is not connected with the testis proper The testis measures 4 by 3 by 2 cm It has the normal color and texture The epididymis has the normal contour and consistency and is free from gross inflammatory or neoplastic changes Sections from the tumor of the tunica show a well circumscribed neoplasm composed mostly of collagenous tissue and a few young fibroblasts forming concentric layers with arrangment of whorls Other parts show fairly large round cells with small nuclei and large cytoplasm There are a few areas suggestive of pseudo palisade formation A few sections stained with Masson trichrome stain show mostly collagenous fibers and a few islands of cells and fibers which take the salmon red stain indicative of nerve fibers and sheaths The H & E stain shows well differentiated cells with no evidence of malignancy Sections from the testis, epididymis, and cord show well preserved seminiferous tubules and normal architecture of the epididymis The pathologic diagnosis was neurofibroma of the tunica albuginea testis (figs 2 and 3) "

The patient was discharged 7 days later with the wound completely healed

The fact that these tumors of the tunica albuginea testis, though rare, simulate malignant tumors of the testis is presented as the chief point of interest The differential diagnosis of malignant and benign tumors of the testicle has always been difficult *The presence of a palpable mass is in itself an indication for* operation

SUMMARY

A case of neurofibroma of tunica albuginea testis is reported

A review of the literature reveals that tumors of the tunica albuginea testis are extremely rare Five other cases, all fibromas, have been collected

Malignant tumors of the tunica albuginea testis have never been reported

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BILATERAL CONGENITAL ABSENCE OF THE VASA DEFERENTIA: CASE REPORT

JESSE G. KESHIN AND BERNARD D. PINCK

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Reports of abnormalities of the epididymes and vasa with testes fully descended in the scrotum are rare. Since such anomalies, when they do occur, are generally unilateral and non-productive of clinical symptoms, it is probable that they are overlooked or observed only at autopsy or in coincidental association with other irregularities of the genitalia or urinary system.

The first satisfactory report of a bilateral anomaly of the seminal tract was recorded by John Hunter in 1755. In an exhaustive review of the earlier literature, Young found adequate descriptions of 12 unusual cases with malformation or absence (partial or complete) of elements of the seminal pathway. Wood reports 5 cases of anomalies of the vas deferens and epididymis associated with cryptorchidism. Radasch and Guizzetti (1918) have presented excellent discussions of the coexistence of renal and genital anomalies. In an extensive post-mortem investigation, Priesel found 8 cases with unilateral abnormalities of the seminal tract. Lespinasse, in 1918, recorded a case of bilateral absence of the vasa although the epididymes were normal. McKirdie and Polkey have described the insertion of a ureter into the seminal vesicle. Individual case reports of congenital absence of one or both vasa have more recently been recorded by Vorstoffel, Jalifier, Dirr, and Balzar and Weber. In summarizing 2 cases and a review of the subject, Young has stated: "Bilateral absence of the vasa deferentia and the very rare absence of the epididymes are serious conditions which produce sterility. The absence of a vas deferens is often difficult to recognize on very careful clinical examination."

From an embryological consideration, the origins of the testis and vas are quite separate and distinct. The testis, with the vasa efferentia and coni vasculosi, has its origin from the genital fold on the mesial side of the wolffian body. The vas, with the body and globus minor of the epididymis, the seminal vesicles, and the ejaculatory ducts are derived from the wolffian duct. In an early stage of development, the duct is closed at both ends but as growth continues, the testis and vas are joined by intermediate tubes. At the caudal end, there is ultimate connection with the prostatic urethra through the ejaculatory ducts. At the caudal end, also, there develops the metanephric evagination to give rise to the ureter and pelvis of the kidney. Thus maldevelopment of the vas due to embryonic arrest without corresponding abnormality of the testes may become prehended. Disturbances in the wolffian duct, however, may result in anomalies of the entire urogenital tract.

A 31 year old white man (J. 74066) appeared at the male sterility clinic of the Post-Graduate Hospital on November 12, 1942 because 3 years of marriage, during which contraception had been avoided, had failed to result in offspring.

Examination of the marital mate in the gynecology clinic had not disclosed significant cause for the fruitless union The family history revealed no hereditary or congenital disease predispositions nor was infertility a complaint of any of the other siblings The patient had suffered no serious illnesses or operations In early childhood he had mumps but no orchitis had occurred, and recovery was uneventful without apparent sequelae Syphilis and gonorrhea were denied by name and symptom The marital and sexual history produced no relevant findings This was his first marriage and was characterized by satisfactory spacing and frequency of intercourse (twice weekly) Coitus was satisfactory, potency was not diminished nor were there excessive episodes of premature ejaculation

The patient was a sturdy, well nourished man Blood pressure was 120/80 and pulse 80 Cephalic and body hair showed normal masculine distribution and texture Skin was warm and dry, of good turgor and elasticity There was no rash discoloration, or eruption Pupils were equal and regular, reacted properly to light and accommodation Eye signs indicative of thyroid dysfunction were absent The thyroid was not palpably enlarged The lungs were clear to auscultation and percussion No cardiac irregularity was discernible No unusual fat deposition or skeletal abnormality was observed The abdomen was soft, flat, and muscular Viscera were not remarkable and no tenderness or spasm was present Extremities were of normal size and configuration, there were no varicosities, tremor, or ulcer The deep reflexes were equal and active

The external genitalia were visibly normal Both epididymes were palpated and although the globus major could be distinguished on each side, no examiner was able to define either epididymis in its entirety Neither vas deferens was palpably distinguishable to most examiners, although one believed a thin cord could be made out close to the external ring on both sides The prostate was of normal size, symmetrical with a well defined median sulcus, consistency was rubbery throughout Seminal vesicles were barely palpable and flat The prostato vesicular secretion showed, microscopically, only a rare white cell, no red cells or sperm

Urinalysis showed a clear, straw colored, acid urine with a specific gravity of 1 006 Tests for sugar, protein, and acetone were negative Microscopic examination was negative Blood Wassermann and Kahn were reported negative Blood urea nitrogen was 14 5 mg per cent, nonprotein nitrogen 32 0 mg per cent, urea ratio 45 per cent The hemoglobin was 15 5 gm, red blood count 4,690,000, white blood count 9,300 with a normal differential count Intravenous urography showed normal function and morphology of both kidneys and ureters Cystoscopy revealed no abnormalities of the bladder Endoscopic examination showed a verumontanum of normal size The ejaculatory ducts could not be seen although it was possible to probe the utricle

Semen analyses were carried out on December 18 and 25 On both occasions no sperm were observed in either specimen

A biopsy from the right testicle, taken according to the method described by

Keshin and Pinck, was reported as follows: "The tubules show marked spermatogenic activity. Adult spermatozoa are present. Interstitial cells are scant and there is interstitial hemorrhage in some areas. Diagnosis: normal testicular tissue with active spermatogenesis." See figure 1.

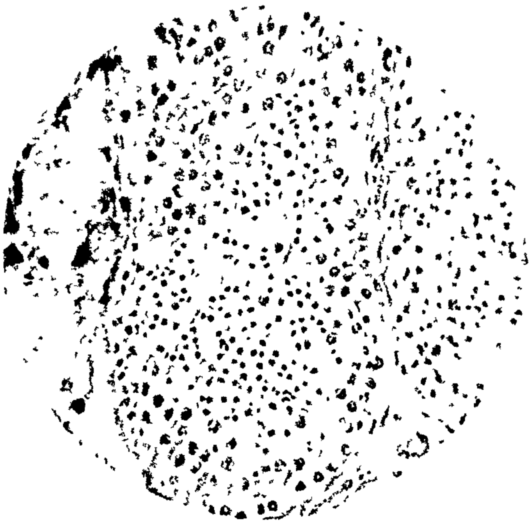

FIG. 1. Biopsy of testicle, showing normal spermatogenesis

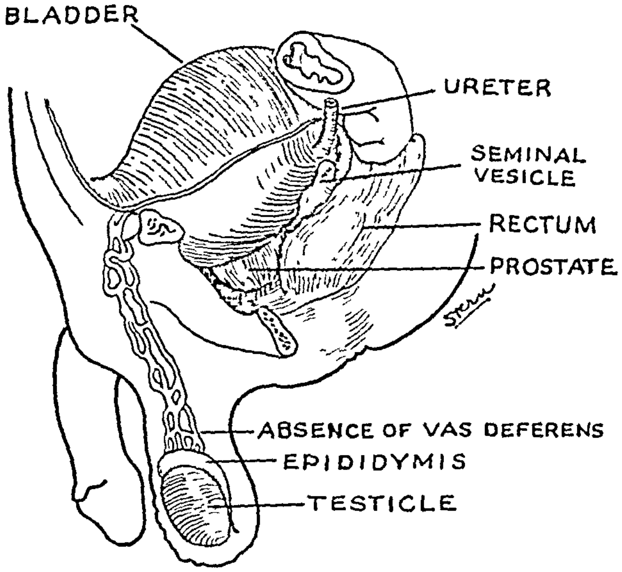

FIG. 2. Showing congenital bilateral absence of the vas

In view of the spermatogenic activity apparent in the testicle with the complete absence of sperm in the semen, it was believed that the problem in this case involved impairment of the vaso-epididymal communication. It was decided to perform scrotal exploration for the purpose of locating the vas and creating, if possible, a vaso-epididymostomy by the Hagner technique.

Operation disclosed that both testicles were of normal appearance. The epididymes had bizarre, abnormal configurations characterized by a normal appearance of the globus major, but the body was thin and shortened, narrowing at its termination to fade into ill defined fascial tissue Distended, tortuous tubules of the globus major were distinguishable The globus minor on both sides was absent (fig 2) Careful and extensive dissection of the spermatic cord bilaterally failed to reveal evidence of a vas

It is of interest that because of the apparent hopelessness of attempting cure of the azospermia, artificial insemination with a donor was suggested and resulted in prompt pregnancy

SUMMARY

Congenital 'absence of the vas deferens is an extremely uncommon genital anomaly The embryologic basis for this condition has been discussed A case of congenital bilateral absence of the vasa deferentia and globi minori is presented with a consideration of previous literature on the subject With the increasing use of testicular biopsy in the study of sterility, opportunity for more frequent discovery of this type of anomaly may be anticipated

We appreciate the guidance and assistance of Dr Clarence G Bandler, director of urology, New York Post-Graduate Hospital, in the presentation of this report

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QUANTITATIVE DETERMINATIONS OF ACID PHOSPHATASE IN THE PROSTATE UNDER VARIOUS NORMAL AND PATHOLOGICAL CONDITIONS: PRELIMINARY REPORT[1]

JOSEPH FISCHMANN, HAROLD A. CHAMBERLIN, RICARDO CUBILES, AND GERHARD SCHMIDT

From the Surgical Department of Tufts Medical School, Boston, Mass., the Urological Department of the Mount Auburn Hospital, Cambridge, Mass., and the Boston Dispensary, Boston, Mass.

With the rapidly increasing interest in cancer research the prostate gland has become one of the most important, if not the most important organ involved in malignancy. There are two reasons for the particular significance of the prostate for cancer research: The rôle of chemical methods in the diagnosis of prostatic malignancy, and the therapeutic response of the malignant gland, as a member of the endocrine chain, to orchiectomy and to estrogen administration. These principles have so far not been paralleled in the diagnosis and treatment of tumors of other origin.

Since Kutscher and Wolbergs' reports on the existence, origin, and properties of the prostatic phosphatase, this enzyme has been investigated extensively. It has been found that this acid phosphatase is probably present in all tissues of the body. However, it is found in largest amounts in the adult prostate. It appears at puberty and is absent in the glands of children. (Gutman.)

After Kutscher and Wolberg discovered the exceedingly high phosphatase content of the prostate in 1935, many investigations have been carried out to determine whether pathological changes in the gland have any influence on the phosphatase content of the blood. These investigations led to the extremely important observation that malignancy of the prostate with bone metastases as a rule, and malignancy without clinical evidence of metastases occasionally, are accompanied by a significant increase of the serum acid phosphatase (Gutman, Sullivan, and Gutman, Gutman and Gutman, Huggins and Hodges.)

In contrast to the many publications on acid phosphatase in the serum, comparatively few data are available concerning the phosphatase content of the prostate under conditions of benign hyperplasia, malignancy, and chronic inflammation. Since such information is indispensable for the understanding of the mechanism responsible for the appearance of prostatic phosphatase in the blood, we undertook a study of the phosphatase content of prostatic tissue in these conditions.

A major technical problem encountered in enzyme determination in prostatic tissue is the difficulty of obtaining fine suspensions, which allow complete extraction from this fibrous organ.

This difficulty recently has been overcome by the development of new tools for the homogenization of tissues, particularly the Waring blendor. This technique of extraction has been used in all our analyses Our average values for prostatic phosphatase are considerably higher than those reported by earlier investigators (Fergusson, Gutman), probably because of the more complete extraction of the enzyme by the technique of homogenization

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., July 3, 1947[1]

For obvious reasons it is difficult to secure large amounts of normal and malignant prostatic tissue because these tissues are usually obtainable only at autopsies An additional difficulty in the evaluation of the results obtained with normal and malignant glands is the fact that postmortem changes have taken place even though these changes are minimal because of the marked stability of the enzyme

As to the group of prostatic malignancies, present day therapy generally avoids complete removal of the prostate This, of course greatly impedes the availability of fresh cancerous prostatic tissue suitable for chemical analysis

TABLE 1

INITIALS	AGE OF PATIENT	WEIGHT OF GLAND	UNITS OF PHOSPHATASE FOUND IN 1 GM WET TISSUE
		gm	
M N	62	54	4200
D R	77	36	2500
W R	65	9 5	665
W H	73	50	2600
G P	64	15	3500
W B	65	12 5	2600
B B	67	12	2060
J McF	68	87	1040
J R	61	36	2400
C B	72	67	2020
S C	54	11	2900
B K	67	12 4	1240
G C	62	23	2600

It should be emphasized that material obtained by transurethral resection, either hyperplastic or carcinomatous, is useless for enzyme determinations, since in our experience such material loses completely its enzymatic activity even though the histological examination reveals the preservation of cell structure Only the group of benign hyperplasias permits the study of a large amount of material as total removal by enucleation is done in the majority of our cases For this reason up to now our analyses comprise mainly material of this group

Our standard technique developed for the determination of acid phosphatase in prostatic tissue is based on the hydrolysis of 3 adenylic acid by the enzyme and the determination of the inorganic phosphate formed during the reaction This substrate, which is now commercially available, is particularly suitable for the determinations because of the rapid rate at which it is hydrolyzed by the enzyme It is split by prostatic phosphatase about 3 times as rapidly as β glycerophosphate This difference might possibly be of value in blood analysis in order to distinguish prostatic phosphatase from acid phosphatases of other origin

Each gland is homogenized in a Waring blendor with 5–10 volumes of water depending on the weight of the gland. The homogenate is kept over night in the refrigerator after addition of a few cc-s of toluene in order to prevent bacterial growth. The suspension is centrifuged next day and the supernatant used for the enzyme determination. $\frac{1}{100}$ of a cubic centimeter of the supernatant is usually sufficient for the determination. The complete extraction of the enzyme was demonstrated by the observation that the supernatant had the same activity as the homogenate. After 15 minutes incubation the mixture was deproteinized with trichloracetic acid, and the inorganic phosphate was determined in the supernatant according to the colorimetric method of Fiske and Subbarow. This technique has the advantage over the King-Armstrong method in that the substrate blank is always practically zero. Owing to the high activity of the enzyme it appeared to be convenient to designate as the unit of phosphatase in prostatic tissue the amount of enzyme required for the formation of 0.1 mg. inorganic phosphate during 15 minutes incubation. One of our units corresponds to 1.1 King-Armstrong units, therefore our figures can be expressed in King-Armstrong units by multiplication with the factor 1.1.

Up to now we have analyzed by this method 40 benign hyperplastic prostate glands. Table 1 shows a few typical examples of the results obtained.

The average number of units of acid phosphatase per gram of tissue in the hypertrophied prostate gland is 2300. While our analyses of normal glands has been limited to only 5 specimens, these findings suggest that the hypertrophic gland produces more acid phosphatase per gram of tissue than does the normal gland. Further investigations will be necessary in order to establish this as a fact.

Since it can be assumed that the production of acid phosphatase is one of the metabolic functions of the prostate gland, our results demonstrate that, at least in this respect, the hyperplastic tissue fully maintains its specific function. The only prostate in our series in which the phosphatase content was conspicuously lower than the average consisted predominantly of fibrous tissue. A similar observation was made on a prostate with the glandular tissue almost completely destroyed by tuberculosis.

Our investigations will be continued and extended to other pathological conditions of the prostate particularly to malignancy and will be published later.

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DISCUSSION

DR WILLIAM P HERBST (Washington, D C) This problem of phosphatase is one of the most vital considerations in the chemistry of the subject we are interested in

On the screen (slide) you see estimations made by A B and E B Gutman of the contents of the phosphatase in the newborn, 4 5 units, and in the adults it runs from 522 to 2274, which is not too far below the essayist's estimates

Huggins demonstrated rather definitely, for instance, that androgen seemed to increase the phosphatase content in the blood and estrogen to decrease it, and that the phosphatase was in most instances—and let me emphasize most instances—a rather dependable indicator as to the clinical trend of the patient

(Slide) The Gomori stain will demonstrate histologically the location and distribution of phosphatase We know that the distribution is not uniform in the gland

Dr Deming has recently demonstrated, after a number of transplants, one generation to another, that phosphatase disappears entirely from the gland, which indicates that our problem concerning malignant aspects of tissue is probably more concerned with the steroid chemistry rather than the enzyme hemistry

Dr Heitz, of the National Cancer Research Institute, who is carrying on the laboratory work in the endocrine laboratory at Gallinger Hospital, has used somewhat similar substrate, only he uses 5 adenylic acid substrate in his reactions rather than 3 He has not up to the present time observed any specificity of action that would indicate that it was prostatic phosphatase rather than others that we are dealing with

He has done some rather interesting experiments on the absorption of phosphatase when tissue is transplanted For instance, transplanted prostatic tissue in the omentum and bones has not resulted in any elevation of the blood levels

He has even produced pulmonary emboli by intravenous injection with no increase of the phosphatase levels of blood, and he has given large amounts of estrogen without increasing it So the phosphatase absorption is interesting

What is in the blood, for instance, or in the tissue that prevents its seeping into the general circulation? That is something we should be interested in

The method that Dr Fischmann and his co workers have used in actually extracting this material is certainly ingenious I don't know of anybody else who has done just that Of course, his objective and the objective of most of those who are interested in the chemistry of malignancy of the prostate is to find some specific reaction that will differentiate a carcinomatous phosphatase from a phosphatase that is not carcinomatous If he can do that, we will all appreciate it

MASSIVE LEIOMYOMA OF PROSTATE: CASE REPORT

D. W. McINTYRE

While small, multiple, myomatous nodules situated in glandular or adenomatous areas are probably much more common than reported, the massive displacement of prostatic glandular structure in whole, or part, by neoplastic proliferation of the stroma, is very rare, most urological writers agree.

CASE REPORT

C. A., a white man aged 71, was admitted to St. Luke's Hospital, Cleveland on November 3, 1946 with acute urinary retention. Symptoms started 10 months ago, when urinary frequency, dysuria and nocturia developed. He had dribbling occasionally. Nocturia and frequency became progressively worse. For the past 4 months he had wet himself frequently and passed pink urine occasionally. Recently, he had to strain at stool. He said that he felt like something was in the rectum. The stools were string-like. He passed blood by rectum. He had not had diarrhea. Except for typhoid fever at the age of 18 years, the past history was essentially negative.

The blood pressure was 170/105; pulse 68; respiration 20; temperature 37.6°. Examination of the head showed nothing remarkable; the lungs were clear throughout. The left border of the heart was in the anterior-axillary line, sixth interspace. A systolic murmur was present over the entire precardium, radiating to the axilla, loudest at the second right interspace. The bladder was percussable and palpable 4 fingers above the symphysis; a spherical mass was present in the midline above the symphysis. The external genitalia were normal. Rectal examination disclosed an enormous mass in the region of the prostate which seemed to partly encircle the rectum and push into the rectum. The top of the mass, which extended upwards into the region of the seminal vesicles, could not be felt. The mass was nodular and fixed.

On admission the white blood count was 9,650; hemoglobin 14.9 gm; blood sugar 102; nonprotein nitrogen 38.2; CO_2 48 per cent; NaCl 620; acid phosphatase 1 unit alkaline phosphatase 5.8 units; Mazzini test negative. Urine obtained by means of a catheter had a specific gravity of 1.015, a trace of protein, and was negative for sugar; microscopic examination showed 2 to 6 red blood cells and 10 to 25 white blood cells per high power field.

A plain x-ray showed both renal and psoas shadows well outlined and normal in appearance, extensive degree of spondylosis of the lumbar spine, considerable calcification of the abdominal aorta and common iliac vessels. No opaque shadows were seen in the renal areas, but there were 2 shadows, one about 4 cm., in the right pelvis overlying the third sacral segment. Another shadow, about 5 cm. in diameter, was seen in the lower left true pelvis.

Intravenous urography showed normal visualization of both renal calyces and pelvis. The right ureter, fairly well outlined, was shown in the lower right true pelvis and was seen to overlie the opaque shadow described in that region The left ureter was only well shown in its upper two thirds

The possibility of a vesical calculus in a diverticulum was considered so cystograms were taken 1 hour after injection of dye No diverticula were seen The shadows previously seen were obscured and faintly visible through the dye There was a marked elevation of the floor of the bladder, also the outline was irregular

An electrocardiogram showed left ventricular enlargement and myocardial disease An x ray of the chest showed that the heart was 35 per cent enlarged There was an elongation and dilatation of the aorta with calcification of the ascending aorta strongly suggesting luetic aortitis A fusiform shadow 6 by 3 cm in the right lung was thought to represent an aneurysm of one of the great vessels

As the catheter was continually blocking, it was decided to do a suprapubic cystotomy A midline incision was made above symphysis for a distance of 4 inches The incision was carried down to the rectus fascia, which was opened The recti muscles were separated in the midline The preperitoneal fat was stripped off the bladder The wall, which was very thick, was opened between Allis clamps Two large and 4 small stones were removed The base of the bladder and the trigone were elevated by a mass which extended from prostate The mass was fixed and nodular The urethra was almost blocked by tumor pressing up on its posterior wall There was a large diverticulum opening off of lower left lateral wall A No 32 Pezzar catheter was inserted No biopsy was taken because the patient was not doing well, and I was afraid of hemorrhage

The patient was discharged November 13, following a smooth convalescence, with suprapubic drainage, to return at a later date for the second operation Because of the enormous size of the tumor, and the fact that it was fixed, I decided to do a transurethral resection

On re admission January 3, 1947, the hemoglobin and blood chemistry were normal The urine was alkaline, contained 1 plus protein, 2 to 3 red blood cells and 4 to 10 white blood cells per high power field Blood sugar was 120, nonprotein nitrogen 36 2, CO_2 52 5, plasma NaCl 569 mg , protein 6 2, bleeding time 4 minutes, clotting time 6 minutes

On January 5, 1947 a transurethral resection was done, 47 gm tissue being removed Considerable bleeding occurred, and was controlled with difficulty A blood transfusion was given

The patient did well until 11 hours postoperative, when the blood pressure rose to 265/140 There was considerable bleeding and both catheters became blocked, and even after evacuating the clots, there was considerable red blood Under sodium pentothal anesthesia, I re opened part of the suprapubic incision and packed with oxy cellulose gauze, which controlled the hemorrhage Both catheters were removed on the sixth day The incision was healed by the eleventh day, and he was discharged January 18

The patient was last seen March 5 He was voiding every $1\frac{1}{2}$ to 2 hours and had a good stream. His main complaint was that if he did not urinate immediately when he had the urge, he might dribble some. The dribbling did not bother him at night. He had 40 cc residual urine. The urine contained 2 to 5 white blood cells per high power field with an occasional clump. Microscopic sections showed the characteristic whorl appearance of interlacing bundles (fig. 1).

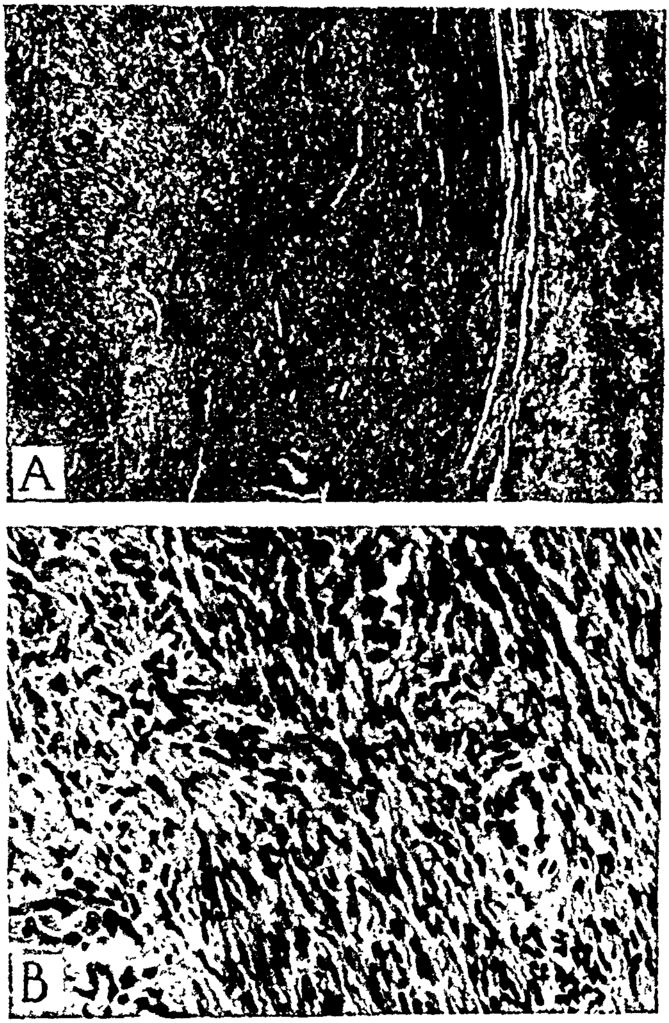

FIG. 1. *A*, Low power view between 2 adjacent nodules. Notice characteristic interlacing bundles of smooth muscle cells with absence of normal glandular tissue. *B*, High power, showing characteristic interlacing smooth muscle bundles.

COMMENT

According to Hinman, benign mesothelial tumors (leiomyoma, fibroma etc.) constitute less than 0.5 per cent of prostatic tumors. MacCallum found 8 prostatic leiomyoma in 14,000 autopsies. Twenty cases of this type of tumor were reported up to 1939 and none since, probably because of restricted writing during the war.

Two types are recognized: one, massive in size, involving and obscuring the prostate, the pelvis and surrounding rectum; the other, mostly pedunculated and may be closely associated with urethra and bladder, and cause obstruction of bladder and ejaculatory ducts

That small leiomyomatous nodules occur more frequently than recognized clinically is stressed by Patch and Rhea These observers, using large whole sections of prostate gland with differential stains found an incidence of 25 per cent in 181 cases

Gross and microscopic pathologic changes are strikingly like those of leiomyomata of the uterus The tissue is firmer than the usual hypertrophy, of a greyish yellow color, and on cross section, has a characteristic whorl appearance of interlacing bundles Encapsulation of small and large nodules is nearly the rule Occasionally the muscle tissue may assume an infiltrating character If growth is intraprostatic, normal glandular tissue may be entirely obliterated or compressed to the periphery of the tumor There may be urethral compression or trigonal elevation When a nodule is located on the periphery of prostatic growth, it may extend upwards towards the seminal vesicles or toward rectum Microscopically, one finds interlacing bundles of smooth muscle cells, with a complete absence of glandular tissue, in leiomyomatous areas A network of interlacing tissue may occur Blood vessels may be infrequent and towards the periphery, or as large vascular channels throughout the tumor Necrotic areas, with calcification and old hyalinized scars, have been noted The growths are usually benign Sarcomatous change is infrequent, even in large glands

Several theories have been brought out, as to the origin of these tumors Blum and Rubritus based their theory on the fact that, since normal elements of prostate are 1) 50 per cent glandular, 2) 25 per cent muscle, 3) 25 per cent connective tissue, they would then designate growths as glandular, leiomyomatous and fibrous The fibromyomata have been recognized, since inception of microscopy However, Virchow, Jacoby and Welman differentiate true leiomyomata from these fibromuscular areas occurring in areas of benign hypertrophy Paul Klemperer states that leiomyomata are adenomata, in which the glands have been abolished

Tandler and Zuckerkandl hypothesize that infection may transform adenomatous masses into smooth muscle Examination of the specimens from the youngest reported cases (4 and 24 years) give no support to this, in that infection was not found in these cases

Virchow and Klebs expressed the view that, when the testicle ceases secreting certain hormones, a proliferation of muscular and fibrous parts of the prostate follows Experimental work of Lower on hormones, however, failed to produce any evidence of muscular hypertrophy

Ewing, in a study of uterine myomata, concludes the essential factor of etiology is in embryonic disturbance in structure of the uterus It would seem that the endocrinal (X) factor, stimulating growth of uterine fibroids, may also effect rudimentary muscular rests within posterior urethra His view is supported by the fact that the embryological anlagen, of the region of the verumontanum and uterus, are essentially the same

Of the 20 previously reported cases, 14 had primarily urinary symptoms, 5 had, chiefly, perineal or rectal symptoms; 1 had the main symptom of painful, persistent erections. One of the rectal cases, reported by Magoun, had a colostomy done for obstipation, with no bowel movement for a week.

Of the 20 reported cases, 12 cases had a suprapubic prostatectomy; 5 cases had a perineal prostatectomy; 2 cases had a combined operation; a transurethral resection was done in 1 case. Many of the operators talk of difficulty in a number of cases of getting a line of cleavage, especially in the large retroperitoneal type. The possibility that tumor regression might follow deep x-ray therapy as in uterine myoma was considered. However, Bugbee tried it in his case, where the tumor could not be entirely removed operatively, without any encouraging results. Seven of the 20 patients died from the operation; a mortality rate of 35 per cent. Five of these died from shock or hemorrhage. Most of these cases were operated upon many years ago and more modern techniques would probably lower mortality considerably.

CONCLUSIONS

While small leiomyomata of the prostate are probably not infrequent, the extensive and massive types are rare, 21 cases having been reported.

Attempt at removal of the massive retroperitoneal type carries a high mortality rate.

These tumors are almost entirely benign; they cause symptoms by pressure.

In this particular case, while the urinary symptoms are under control, the patient still complains considerably of constipation. This, I am sure, comes from rectal compression. If his symptoms increase, I intend to give x-ray therapy.

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PROBABLE METASTATIC CARCINOMA OF THE MALE BREAST FOLLOWING STILBESTROL THERAPY: CASE REPORT[1]

F. HAROLD ENTZ

Since 1941 the use of estrogens in patients with carcinoma of the prostate gland has become quite universal. The medical literature is filled with a variety of reports attesting to the efficiency of this medication as well as to its inefficiency. The side effects of this drug have also been very ably described in the literature. In fact, the most useful and accepted clinical criterion for the assimilation of the estrogen is its effect on the nipple and breast which early become tender and hypertrophied. The case about to be reported is one in which this usual side-effect of stilbestrol did not follow the ordinary pattern but proved to be rather bizarre, namely, the development of a malignancy of the right breast during the therapy. The possibility of this complication has been noted in the female, especially in those women with a familial tendency toward carcinoma. However, I have found no particular reference to such a complication in a patient with carcinoma of the prostate gland under similar therapy and it would therefore seem worthwhile that it be reported.

CASE REPORT

A white truck driver 49 years of age was referred to me on March 20, 1944. The chief complaint was frequency of urination associated with an increased difficulty requiring considerable straining at times. This had gradually increased in severity during the preceding 4 months. He had a low backache most of this time with a radiation down both thighs simulating sciatica. There was moderate anorexia with a loss of 30 pounds of weight in the preceding 6 weeks. The bowels were mildly costive. Other systems were relatively symptomless. There was no familial history of carcinoma.

Examination revealed some emaciation, blood pressure 148/84, pulse of good quality and regular. The lungs were clear to percussion and auscultation. The breasts were normal to appearance and palpation. There was no palpable mass in the abdomen. The external genitalia were normal. The prostate was 3 plus enlarged, irregular, fixed to the pelvic wall, and typically stony hard. He was found to have 175 cc. residual urine which showed a specific gravity of 1.024, a trace of albumin, no sugar, and 6–8 pus cells to the high power field microscopically. The blood count showed 64 per cent hemoglobin, 3,450,000 erythrocytes and 7,900 leucocytes with 68 per cent polymorphonuclears and 32 per cent mononuclears in the differential. A plain x-ray showed a diffuse milky increase in density of the lumbar spine and pelvis, with irregular areas of destruction. This was considered quite typical of extensive metastatic carcinoma of the prostate. See figure 1.

The obvious clinical diagnosis in this case was carcinoma of the prostate gland with extensive metastases to the pelvic girdle. The physical findings did not seem to warrant hospitalization and resection of the gland at this time. It was decided, however, to try estrogen therapy for a short period.

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[1] Read at annual meeting, North Central Section, American Urological Association, Rochester, Minn., November 1, 1946.

He was instructed to take 3 mg. of stilbestrol 3 times a day and when next seen on March 28, 1944, eight days later, he reported that he had improved very much. The appetite was better and he noted less difficulty in urination. The pain was much less severe. Notation was made that the prostate seemed less hard but otherwise unchanged. At this time there were no nipple or breast manifestations commonly seen in cases during the use of stilbestrol. The stilbestrol was decreased to 4 mg. per day. He was next seen on May 1, 1944, at which time he reported that he had regained much of his weight and strength, no longer needed a helper on his cream route and had no more backache. There was no residual urine at this time. The breasts were only moderately enlarged but the nipples quite tender.

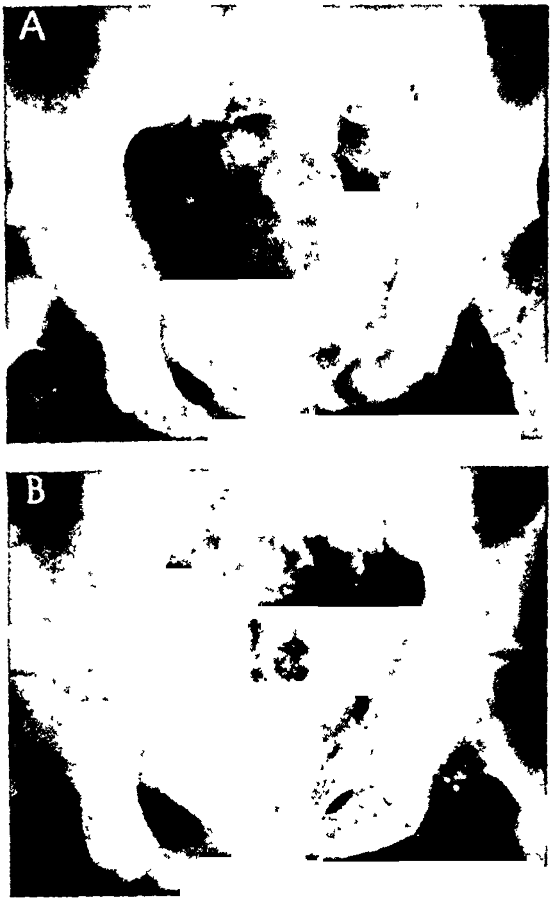

FIG. 1. *A*, X-ray taken at start of therapy. *B*, After 16 months of therapy.

The stilbestrol was gradually decreased by the patient until June 6, 1944, when ½ mg. twice each day maintained a very moderate nipple tenderness. The prostate, though not quite so hard as on first examination, was still fixed. The testicles were both about one-third their former size and soft.

He was seen occasionally during the rest of the year with continued general improvement and not until April 20, 1945, did he show any definite evidence of regression At this time he complained severely of "rheumatism" in his back which required codeine for relief Anorexia recurred with a loss in weight of 20 pounds The breasts did not show any further change He had no urinary distress and no palpable bladder dullness The plain x-ray taken on June 11, 1945 showed an increase in density of all the bones of the pelvis with a marble like appearance and a few areas of reduced density

His course was rapidly downhill from this time until his death on August 18, 1945, seventeen months after diagnosis and institution of treatment Both breasts, which were moderately hypertrophied under the stilbestrol therapy, were first noted as being nodular on July 12 and 2 weeks prior to his death, nodules were palpable in the right axilla No nodules were palpable in left axilla at this time At no time were there noted any palpable subcutaneous glands A numbness of the face and complete paralysis of both lower extremities developed 1 week prior to death at which time complete retention of urine occurred

A complete autopsy was certainly indicated in this case but such was not permitted A "biopsy" of the right breast was done and with rather bizarre findings It does not show conclusive evidence of either carcinoma of the breast nor typically malignant prostatic tissue It is lacking in the crablike appearance of a primary carcinoma of the breast but it does show some of the hypertrophic changes seen in the breasts of patients under stilbestrol therapy It has much more the encapsulated appearance seen so often in prostatic malignancy Several pathologists have seen the slides and all agree it is malignant but do hesitate somewhat to label it definitely as metastatic carcinoma originating in the prostate See figure 2

The report from Col J E Ash to whom sections were also sent is as follows " It is our feeling that these lesions represent a small cell carcinoma, probably from the prostate These cells are spindle shaped and seem to be invading the breast tissue The ductal elements are compressed and surrounded by dense fibrous connective tissue and do not appear to show any hyperplastic changes The consensus is that this represents a metastatic lesion to the breast, probably secondary to the carcinoma of the prostate, which was diagnosed clinically "

My method of treating these unfortunate victims of carcinoma of the prostate contains no original ideas I have relied almost entirely on the use of stilbestrol rather than orchiectomy The patients who are not in immediate need of surgery for relief of bladder neck obstruction are started on stilbestrol, usually 9 mg each day This dosage is continued until the patient experiences a tenderness of the nipples at which time the dosage is decreased to that amount which will just maintain a mild residual tenderness They are further instructed to vary this at will in order to maintain such tenderness

While my series is not of such size as to warrant definite conclusions, various observations have been made The results in my cases do not justify any statement relative to its curative value However, the relief from pain in approximately 65 per cent of these patients certainly justifies its use No one seems to

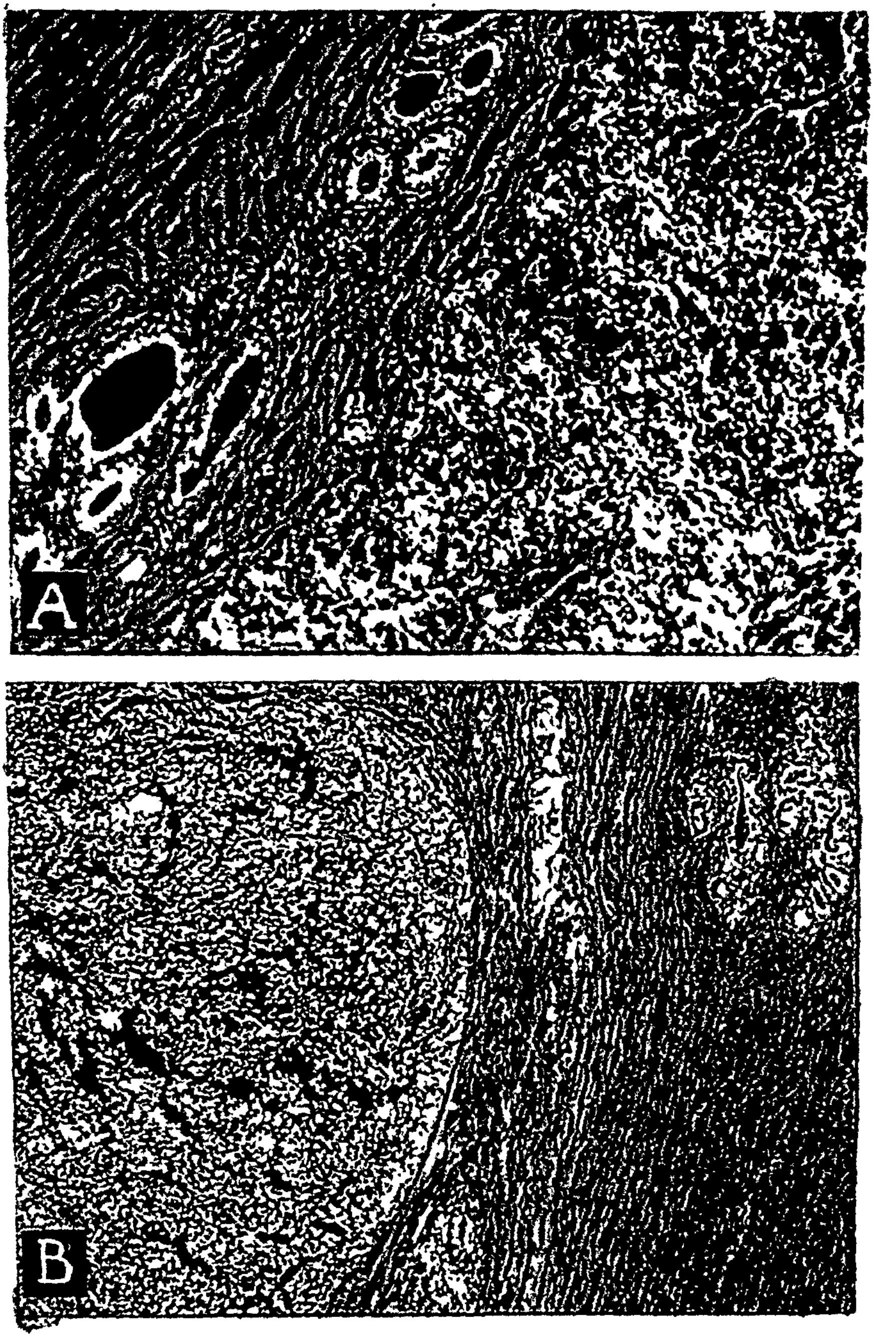

Fig. 2. *A*, Photomicrograph of breast tumor, X 125. *B*, Photomicrograph of breast tumor, × 75.

have answered the question as to the reason or reasons for failure in these other 35 per cent of cases. In my experience the younger the individual who has sufficient symptoms to cause him to seek medical advice, the less likely will the results be favorable, as attested by the present case If this metastatic lesion were enhanced in any manner by use of these estrogens, it would perhaps be advisable to treat the younger patients by castration rather than with the estrogens and thereby obviate the possibility noted in this case, rare though it may seem The degree of malignancy or the type of malignancy might harbor the answer to this question but as yet, this does not seem to be settled

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and fixed. X-rays revealed metastases in the ribs, pelvis, and left femur at the distal end. His blood urea had come down to 32.

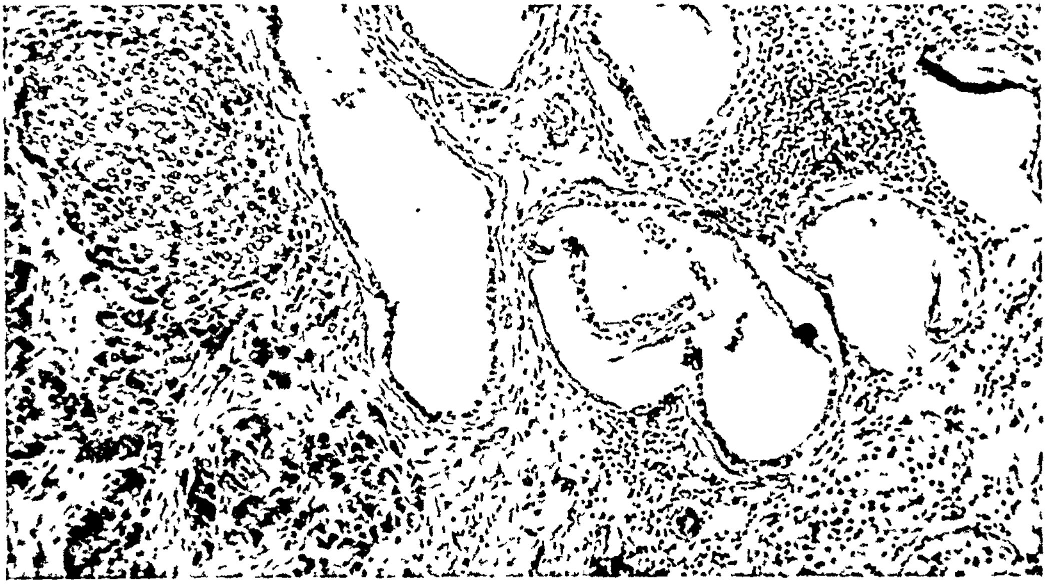

FIG. 3. Higher magnification of area shown in figure 1

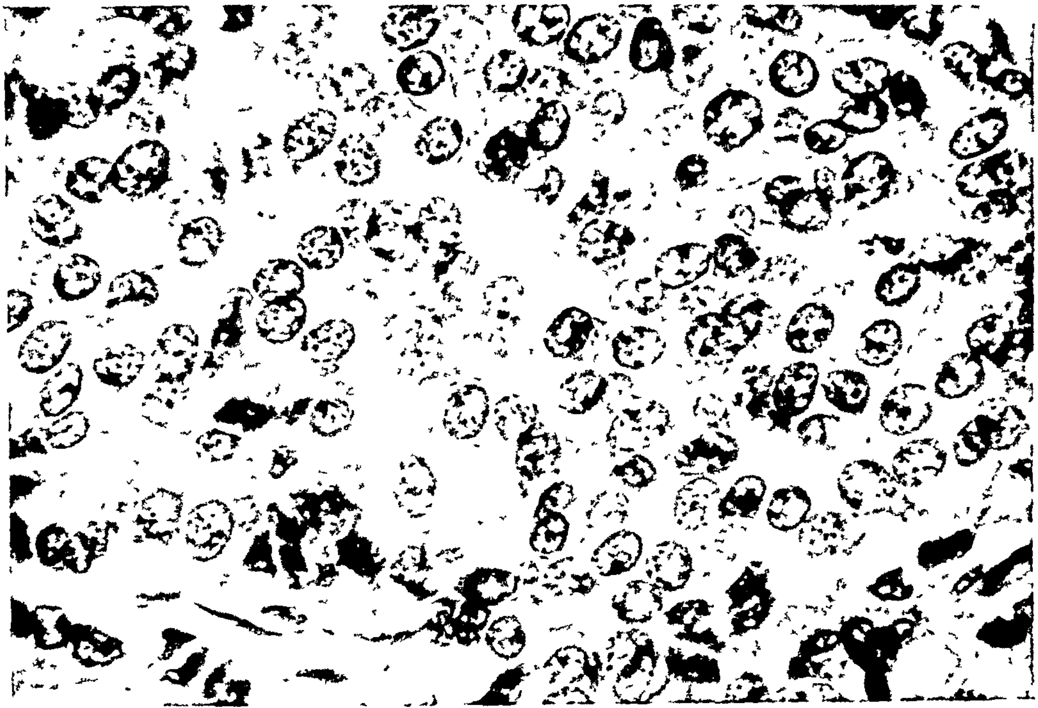

FIG. 4. Showing details of tumor cells

DISCUSSION

The first report of metastasis from the prostate to the testicle was by Semans in 1938. His case had metastases to the sacrum, lumbar vertebrae, and right testis. This diagnosis was made at autopsy, not clinically. The epididymal veins and lymphatics were involved, but not the efferent ducts.

The second case was reported by Helfert and Pinck in 1944. The left testicle was involved in their case, the diagnosis being made after bilateral orchiectomy for carcinoma of the prostate, not clinically. The invasion was chiefly interstitial, as in the previous case.

Both authors believe that metastasis occurred by arterial embolism, and we consider that likely in our case. We agree with Helfert and Pinck that the presence of coincident metastasis elsewhere, as noted in all three of these cases, supports the idea of arterial spread. Humphrey states that extension of prostatic carcinoma along the vas deferens is a rare occurrence.

SUMMARY

The third reported case of metastasis from carcinoma of the prostate to the testicle is herewith submitted. It is of interest that such a diagnosis has not been reported as having been made clinically.

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THE USE OF GLYCINE SOLUTION AS AN IRRIGATING MEDIUM DURING TRANSURETHRAL RESECTION

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Considerable interest has been aroused in the problem of the patient who, following a transurethral prostatectomy, manifests an anemia not commensurate with the operative blood loss, marked oliguria or anuria, loss of appetite, progressive nitrogen retention and jaundice.

Creevy believes this syndrome is due to intravascular hemolysis and has accredited McLaughlin with the suggestion that it is produced by water, used as an irrigating medium which has passed into the prostatic venous plexus during transurethral resection. Circumstantial evidence was provided by Foley (personal communication to Creevy) who observed spurts of red urine from the ureteral orifices during the course of a transurethral prostatic resection, and who subsequently found a high level of hemoglobin in the plasma of the patient.

In adhering to the principle of complete removal of the adenomatous gland by the transurethral route, the surgeon occasionally oversteps bounds and incises into the periprostatic venous plexus, with the result that brisk bleeding occurs. In such an instance the resectionist, in order to facilitate vision for the maintenance of hemostasis, may be forced to raise the level of the water reservoir inordinately high, thereby forcing the irrigating fluid into the venous system. Varying amounts of hemolysis might result from this course of events.

In proof of his thesis, Creevy found the average postoperative plasma hemoglobin level to be 59 mg. per cent in 9 patients upon whom he had performed transurethral prostatic resection using distilled water as an irrigating medium; whereas the control series exhibited no more than the average normal plasma hemoglobin level of 5+ mg. per cent.

Oliguria of this type has not been observed in any of the resected patients in the University of Michigan Hospital during the past 16 years. However, it is not at all unlikely that some of the postoperative morbidity which has occurred may have been due to unrecognized minor manifestations of the syndrome. Investigations have been made to determine if any subclinical hemolysis was taking place under conditions similar to those described by Creevy. Pre- and postoperative samples of plasma or serum were drawn through an 18 gauge needle, which along with its syringe had been previously cleansed with sterile isotonic saline. A pink to red discoloration of the plasma or serum in a sample of blood drawn 3–20 hours postoperatively was considered as indicative of intravascular hemolysis. In a group of 15 patients studied in this manner, there was no evidence of gross hemolysis in the preoperative samples, but in 3 patients there was gross hemolysis in the specimen examined postoperatively. None of the patients manifested any clinical signs of intravascular hemolysis. A serum bilirubin was determined in one of the patients exhibiting hemolysis and this was found to be

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

0.1 mg. per cent. Elevation in serum bilirubin is not to be expected after minor intravascular hemolysis, for Ottenberg and Fox found no detectable rise in its level even after the intravenous injection of 5 gm. of free hemoglobin.

Granting the mechanism by which intravascular hemolysis is induced during the course of transurethral prostatic resection, interest is then attracted to the concomitant hemoglobinemia and to the hemoglobinuria with which it is so often associated.

In a review of the subject, Ross states that normally a level of 2–5 mg. per cent of "heme" containing pigment exists in plasma as a result of intravascular breakdown of erythrocytes. There appears to be a definite renal threshold for the excretion of hemoglobin, determined by the degree of saturation of the renal tubular cells. Yuile found hemoglobinuria where the plasma level exceeded 100 mg. percent; Gilligan et al. found it above 135 mg. per cent.

The mechanism by which renal damage results from severe intravascular hemolysis is poorly understood, but several factors bear mention. Although Gilligan et al. showed that intravenous administration of 16 gm. of pure hemoglobin to normal subjects produced no significant renal impairment, Mason and Mann demonstrated spasm of the renal blood vessels subsequent to intravenous injection of hemoglobin.

It was believed by many investigators that hemoglobinuria in the presence of an acid urine resulted in the formation of acid hematin which mechanically blocked the renal tubules. However, Bing working with dogs, showed no histologic renal lesions, and no significant variation in renal function after intravenous infusion of large amounts of hemoglobin and myoglobin, even with the blood at a pH of 6.9. Infusion of methemoglobin did produce demonstrable renal impairment. Pigmented tubular casts were found only in acidotic animals after renal failure had been initiated. He believes the acidosis accompanying the anuria may affect the respiratory enzymes of the tubular cells, accounting for impaired renal function. This factor would provide the indication for alkalinization when hemoglobinuria exists. He further believes that the renal vasoconstriction induced by hemoglobinemia may result in ischemia of the tubular cells accounting for their diminished function.

It is Ross' opinion that fatal renal damage is probably produced by shock-like levels of blood pressure, and by severe and prolonged reduction of blood flow through the kidney, the latter being accentuated by hemoglobinemia. Where an associated marked reduction of alkaline reserve exists, the formation of methemoglobin in acid glomerular filtrate may further add to already existing tubular damage.

In selecting an isotonic irrigating solution which will eliminate the risk of intravascular hemolysis, several properties must be considered:

1. It must be either non-electrolytic, or very weakly ionized, for a highly ionizable substance such as sodium chloride allows dispersion of the high frequency current, thereby inhibiting its cutting properties.
2. It must be non-toxic either by local tissue action or when administered intravenously.
3. It must be transparent so as not to interfere with visual acuity during the

or marked blood loss acting upon kidneys damaged by chronic pyelonephritis and/or arteriosclerosis, may result in a clinical syndrome which is manifested clinically by anemia, oliguria or anuria, and uremia. This syndrome may end fatally.

The phenomenon due to this cause can be prevented by the use of any isotonic non-electrolytic irrigating solution.

A 2.1 per cent solution of glycine, an amino acid, is isotonic and has been found to satisfy the proposed criteria; it has been employed successfully in 45 transurethral prostatic resections without demonstrable gross evidence of intravascular hemolysis.

A 1.1 per cent solution of glycine, while not isotonic, has been found nonhemolytic in vitro, and has been used in 30 resections without producing hemolysis. The use of the lower concentration is economical as well as safe so its employment as an irrigating solution during transurethral prostatic resection is advised.

Note: Since this paper was read, the 1.1 per cent solution of glycine has been used in over 200 additional patients undergoing transurethral prostatic resection with no ill effects and without demonstrable hemolysis.

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THE IMPORTANCE OF HEMOLYSIS DURING TRANSURETHRAL PROSTATIC RESECTION; A CLINICAL INVESTIGATION[1]

C. D. CREEVY

Every urologist who strives to resect the prostate gland transurethrally down to the surgical capsule knows that the operation is sometimes followed by uremia and other disturbances which are difficult to explain.

In a characteristic reaction one sees a chill and cyanosis during or shortly after operation; nausea and vomiting often ensue, and oliguria and azotemia are soon evident. A mild, non-obstructive jaundice and an anemia more severe than one would expect from the actual loss of blood are typical, and hypertension may occur later.

Postoperative uremia may follow such evident causes as acute pyelonephritis, prolonged severe hypotension (anesthesia, hemorrhage, or surgical shock); reactions to the transfusion of incompatible blood or to the administration of sulfonamides; or trauma to the ureteral orifices with resultant hydronephrosis. However, cases occur in which all of these factors except the loss of blood can be excluded.

Since the type of uremia under discussion seems to occur most often when considerable blood has been lost during or after operation, one is tempted to attribute the azotemia to spasm of the renal blood vessels. Phillips et al. have demonstrated an almost complete cessation of glomerular blood flow during severe hemorrhage in dogs, even though the blood pressure is maintained artificially above shock levels. Van Slyke has described a similar situation in surgical shock, and has pointed out that impairment of renal function may become irreversible if the hypotension lasts for some hours. Corcoran and Page have observed oliguria and azotemia in dogs after severe hemorrhage even with prompt replacement of the lost blood. They have attributed the renal impairment to vasospasm mediated by some humoral mechanism, since it occurs even if the kidneys are denervated first. Bingham has suggested that bilateral renal cortical necrosis may be due to renal ischemia from vasoconstriction.

While these ideas explain some features of the hitherto obscure uremia which may follow transurethral resection, they do not account for the mild, non-obstructive jaundice which usually accompanies it, nor for the fact that an anemia out of all proportion to the amount of blood lost by hemorrhage is often demonstrable as early as 24 hours after operation.

The explanation of these phenomena is probably to be found in the suggestion recently made by Dr. J. L. Emmett to the effect that the sterile water used as an irrigating fluid during transurethral resection may enter the prostatic veins and produce hemolysis, thus damaging the kidneys exactly as does a transfusion or marked blood loss acting upon kidneys damaged by chronic pyelonephritis and/or arteriosclerosis, may result in a clinical syndrome which is manifested clinically by anemia, oliguria or anuria, and uremia. This syndrome may end fatally.

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[1] Read at annual meeting, the American Urological Association, Buffalo, N. Y., July 2, 1947.

The phenomenon due to this cause can be prevented by the use of any isotonic non-electrolytic irrigating solution.

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at 600 cc. Because of this, and despite the fact that the systolic blood pressure did not fall below 120 millimeters of mercury, 500 cc of human plasma were given intravenously; and an oxygen tent was used immediately after operation because of cyanosis mistakenly thought to be due to pentothal sodium. He remained drowsy and restless all day. That evening, his plasma was found to be dark red in color, although no quantitative estimate of free hemoglobin was made; 500 cc. of 5 per cent sodium bicarbonate were given intravenously.

The fluid intake during the day of operation totalled 2000 (exclusive of the plasma) and the urine output 550 cc. The blood pressure remained above 120.

On the morning after operation the patient was nauseated; the urea nitrogen was 54 mg. per cent, and the hemoglobin had fallen from 87 to 50 per cent (Sahli), with a red blood count of 2,630,000, although the total loss of blood during and after operation could not possibly have exceeded 1000 cc. Slight jaundice was noted, but no serum bilirubin determination could be made because of the hemoglobinemia, which was still considerable. The stools were normal in color. The fluid intake on the first postoperative day was 2000, and the urine output was 825 cc.

On the second postoperative day the hemoglobinemia had disappeared and the plasma was straw colored, but the urea nitrogen was 70 and the urine output, with a fluid intake of 2250, was 440 cc. Five per cent sodium bicarbonate was again given, and was followed by a half liter of matched, citrated whole blood (his first transfusion).

The oliguria continued, and fluids were administered conservatively. By June 4 the urea nitrogen was 109, the creatinine 5.2, the CO_2 combining power 55, and the plasma proteins were 5.8. He had continued apathetic and had developed moderate generalized edema; the blood pressure was 190/102. Peritoneal lavage as described by Fine, et. al. was instituted on June 5, and he was transfused a second time with citrated blood, preceded by 5 per cent sodium bicarbonate. Penicillin was given intramuscularly and streptomycin was added to the lavage fluid. Auricular fibrillation appeared and he was digitalized by Dr. George Fahr. By June 9, the urea nitrogen had fallen to 67 mg. per cent, and the edema had diminished, possibly because 5 per cent glucose had been added to the fluid used to lavage the peritoneum (table 1). However he died, apparently from pulmonary edema, on June 9. The maximum urine output in any one 24 hour period after operation never exceeded 825 cc.

Autopsy was performed shortly after death by Dr. A. J. Hertzog, pathologist at St. Barnabas Hospital, with the following results:

Nutrition was good. The scrotum and ankles were edematous. There were surgical wounds 6 cm. long in each lower abdominal quadrant. The sclerae were icteric. There was a liter of cloudy fluid containing flecks of fibrin in the peritoneal cavity. The peritoneal surfaces were clean.

The left pleural cavity was obliterated by old adhesions, and the right contained 1½ liters of clear, straw-colored fluid. There was mild coronary sclerosis, with cardiac hypertrophy and dilatation. The lungs exhibited basal atelectasis as well as moderate edema and emphysema.

The liver weighed 2075 gm. and the cut surface was a mottled reddish brown.

The gallbladder was thin walled but contained many stones. The bile ducts were patent. The gastro-intestinal tract, pancreas, and adrenals appeared normal.

The kidneys were enlarged (215 and 235 gm.) but of normal consistency. Both cortex and medulla were thick, and the markings were distinct. The cut surfaces were dark red and homogeneous. The pelves and ureters were not dilated.

The bladder and prostatic cavity showed the effects of the recent operation. The prostatic capsule had been perforated on the right posterior wall, but there was no extravasation or periprostatitis.

The central nervous system was not examined.

TABLE 1. *Chart of fluids and metabolites*

	OPERATION												
	May				June								
	28	29	30	31	1	2	3	4	5	6	7	8	9
Fluid intake, cc.	2000	2000	2250	3545	2220	1010	2550	2150	1550	1500	0	85	
Fluid output, cc.	550	825	440	600	550	350	500	450	500	450	500	400	
Blood urea N_2	21	49	79	66	74	62		109		92	87	77	67
Peritoneal lavage													
Input, cc.									8250†	22700†	23800*	23200*	14100*
Output, cc.									6900	22100	25100	24350	14700
Urea N_2, gm.									2.3		10.89		
Total N_2, gm.										24.3		38.8	

† Hartman's solution.
* 5% glucose added.

Microscopic examination: Lungs: Alveoli distended and contain a moderate number of red and mononuclear cells. Liver: Slight atrophy of central cord cells. Prostate: Necrosis of cut surface with acute exudative inflammation; partially organized thrombi in larger veins. Myocardium: Some fragmentation of muscle bundles and separation of fibers. Kidneys (fig. 1): Pigmented casts filled many collecting tubules. The epithelium of the convoluted tubules was flattened and their lumina dilated. The interstitial tissues were infiltrated by lymphocytes and plasma cells. There was mild subintimal hyalinization of the arterioles, and the glomeruli were normal.

Conclusions: 1) Recent transurethral prostatic resection; 2) postoperative hemoglobinemia; 3) obstruction of the renal tubules by pigmented casts (hemoglobin?), and toxic changes in the tubules; 4) uremia (clinical); 5) hypertrophy and dilatation of the heart from hypertension; 6) pulmonary edema; 7) right hydrothorax; 8) chronic passive congestion of the liver; 9) cholelithiasis; 10) ascites (from peritoneal lavage).

It is evident that the reaction which followed transurethral resection in this patient was identical, both clinically and pathologically, with that which follows a transfusion with incompatible blood. Figure 2, *A* and *B* shows sections of the left kidney of another patient subjected to renal biopsy on the third day of anuria which followed the transfusion of incompatible blood, and are included for comparison. Differences in appearance are due in part to difference in the ages of the patients (68 and 21), and to the difference in the stage of the reaction (twelfth and third day).

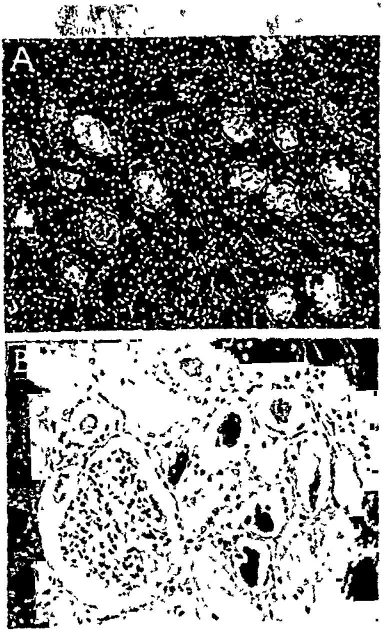

Fig 1. *A*, Pigmented casts and [illegible] urethral resection. B K., aged 68. Low power, benzi[illegible] of *A*.

REVIEW OF THE LITERATURE

It has been known for a long time that transfusions of incompatible blood may produce hemoglobinemia, hemoglobinuria, and renal insufficiency with oliguria or anuria. According to Flink, hemoglobinuria after the transfusion of incompatible (heterologous) blood was first described in [illegible] 1667. The renal [illegible] are well known. [illegible] described in blackwater fever by Barratt and

Yorke and by de Haan; after severe burns by Shen, Ham, and Fleming; after crush injuries (myoglobin rather than hemoglobin) by Bywaters and Beall; after obstetrical mishaps associated with infiltration of the uterine muscle with blood by Paxson, Golub, and Hunter; and after the transfusion of incompatible blood by many investigators. Similar changes have, according to Lucké, been found in the kidneys after traumatic muscular ischemia, heat stroke, sulfonamide intoxication, and poisoning with certain vegetable and chemical agents. Lucké has recently reviewed the literature on these points and has reported a number of cases occurring in the army during World War II; he has suggested the term "lower nephron nephrosis" for renal lesions in all the categories listed above.

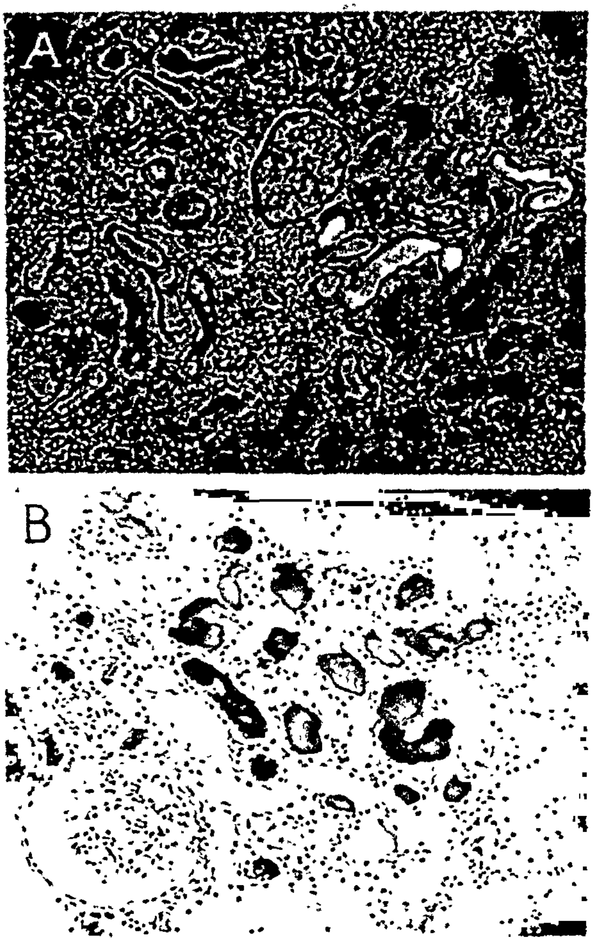

FIG. 2. *A*, Biopsy of kidney 3 days after transfusion with incompatible blood. J. T., aged 21. Lower power, benzidene stain. (Patient recovered.) *B*, Higher magnification of *A*.

The changes in the kidneys in these conditions include vacuolation, necrosis, and desquamation of epithelium in Henle's loops and the distal convoluted tubules; pigmented casts are found in Henle's loops and in the convoluted and collecting tubules, and hemosiderin granules are seen in the convoluted tubules. Edema and cellular reaction are found around the more severely damaged tubules. Precipitated protein may be found in the glomerular capsules, which are not dilated, although the tubules proximal to the casts may have dilated lumina and thinned epithelium.

There has been controversy over the nature of the pigmented casts, which have been called hemoglobin, methemoglobin, and acid hematin, but Flink states that their composition is as yet unknown. They contain no iron, but give a positive benzidene reaction. There has also been disagreement over the exact cause of the renal insufficiency which accompanies the more severe lesions. Baker and Dodds and others have thought that the pigmented casts consisted of acid hematin and obstructed the nephron, a view which has been widely accepted; others however believe that the hemoglobin or some product thereof exerts a direct toxic effect upon the epithelium of the renal tubules, and that the pigmented casts are shed by the tubular cells as the result of the action of the toxic agent, plugging being unimportant. Anderson, Morrison, and Williams, and Corcoran and Page have suggested that hematin is the toxic agent.

It has been shown experimentally that similar changes in the kidney follow the intravenous injection of solutions of hemoglobin by Levy, and of laked red blood cells by Barratt and Yorke; the latter found that the renal lesions were less severe if the stroma of the red cells were first filtered out. The arrival of the hemoglobin in the kidney evidently produces a vasoconstriction, since definite shrinkage of the organ has been detected immediately after intravenous injection of laked red cells in the dog by Levy, and of hemoglobin solutions in the frog by Mason and Mann, and in the dog by Hesse and Filatov. This may be of some importance in renal insufficiency after transurethral prostatic resection, especially if the vasoconstriction from free hemoglobin is added to that already or concomitantly produced by hemorrhage or hypotension, the presumption being that the resultant reduction in renal bloodflow prolongs the contact between the hemoglobin and the kidney, thus enhancing both its toxic effects and the opportunity for mechanical plugging of the tubules. It seems possible that, in such circumstances, a relatively mild hemoglobinemia might be followed by damage to the kidneys, especially if they were previously abnormal (arteriosclerosis, pyelonephritis, hydronephrosis) as is so commonly the case in prostatism.

Flink has pointed out that hemoblobin is a threshold substance which is excreted by the glomeruli and reabsorbed by the tubules. Monk and Yuile found that the threshold in the dog varied from 80 to 150 mg. per cent; Gilligan, Altschule, and Katersky estimated it at 135, and Ottenberg and Fox at 288 mg. per cent or higher in man.

It is well established that a considerable quantity of hemoglobin must be present in the plasma before the kidneys are damaged. Sellards and Minot observed no untoward reaction after the intravenous injection into the human of a solution made by hemolyzing 33 cc of packed red blood cells. O'Shaugnessy, Mansell and Slome found no impairment of renal function after the intravenous injection of 50 gm. of hemoglobin into a man, although it was followed by a hemoglobinuria lasting 30 hours. Altschule and Gilligan found the plasma hemoglobin to be 500 mg. per cent 24 hours after the onset of a severe hemoglobinuria in a patient whose nonprotein nitrogen subsequently rose to 90 mg. per cent, but who later recovered. Fairley and Bromfield observed 3 patients who died in anuria from blackwater fever; their plasma hemoglobins were 3.6, 4.6, and 5.1 per cent (3600 to 5100 mg. per cent). Flink found that all of his dogs which developed severe renal insufficiency after the intravenous injection of hemoglobin solutions or of laked blood had levels above 3700 mg. per cent at the conclusion of the injection.

He found that about one-third of the hemoglobin injected intravenously into dogs could be recovered in the urine; it had ordinarily disappeared from the plasma in 72 hours, the remainder presumably having been taken up by the cells of the reticuloendothelial system.

The idea of Baker and Dodds that the harmful effects of hemoglobin upon the kidney can be averted by making the urine strongly alkaline beforehand, thus rendering the hemoglobin more soluble and preventing blockage of the renal tubules, has been widely accepted, and alkalinization before transfusion has been practiced extensively. However, others doubt the efficacy of alkalis. Thus, Foy and Kondi saw anuria in blackwater fever despite an alkaline urine, and Maegraith and Havard found that therapy with alkali did not reduce the mortality of blackwater fever. Walker has stated that alkalinization is of doubtful or no value even when given early for the hemoglobinuria of severe burns; Bywaters is skeptical of its merits in crush injuries; and Flink found that preliminary alkalinization of the urine of the dog did not influence the incidence nor the severity of the renal lesions which followed the injection of hemoglobin or of laked red blood cells. Kirsner and Palmer have observed impaired renal function to accompany alkalinization in peptic ulcer. It appears, therefore, that alkalinization is probably harmful rather than helpful in hemolytic reactions, since death is usually due to renal failure.

It seems safe to assume that the deleterious effects of transfusions with incompatible blood are due to the transport to the kidneys of free hemoglobin or one of its breakdown products, which damages the renal tubules either by some direct toxic action, by the production of vascular spasm, by plugging of the nephron, or more probably by all three. It has been claimed by Maegraith, Havard, and Parsons that anoxia resulting from the vasospasm induced by the toxic agent may be responsible for much of the tubular damage.

Dunn, Gillespie, and Niven have suggested that the oliguria which accompanies these lesions is due to unselective absorption of glomerular filtrate by the injured tubules. It appears evident that the changes in the renal tubules can be produced by the intravenous injection of solutions of hemoglobin, and by laked blood, and that they also occur in other hemoglobinurias (blackwater fever, severe burns, and crush injuries), although in the last instance the toxic factor appears to be myoglobin. If hemoglobinemia alone is to damage the previously normal kidney, it must be very severe.

CLINICAL APPLICATION TO TRANSURETHRAL PROSTATIC REACTION

It is customary to use sterile tap or distilled water as the irrigating fluid in transurethral resection. During the course of the operation, especially if it is reasonably complete, many good sized veins in and around the prostate may be opened. The resulting hemorrhage necessitates running the water in at a rapid rate (hence under some pressure) in order to wash the blood away from the operative field sufficiently to permit the operator to see what he is doing. It is therefore easy to understand how the water, probably by now containing blood already hemolyzed in the bladder, may enter the venous system and there produce hemolysis. Indeed, one may readily see hemolysis occur as the stream of irrigating fluid strikes the blood issuing from the cut surface of the prostate. There is thus no doubt that conditions favorable to a hemolytic reaction may occur during transurethral resection.

TABLE 2. *The effect of various non-urological procedures on the free hemoglobin of the plasma*

	BEFORE	AFTER
A. Intravenous solutions, 21 cases		
Lowest	0	0
Highest	28	15
Average	5.5	5.2
B. Diathermy without irrigation (neurosurgery), 8 cases		
Lowest	0	0
Highest	39	14
Average	5.5	3.4
C. General surgery, 13 cases		
Lowest	0	16
Highest	23	16
Average	4	8

In the face of these facts, studies were begun along several different lines. Dr. E. T. Bell, Professor of Pathology, kindly reviewed sections of the kidneys in 6 patients who came to autopsy after death in uremia following transurethral resection at the University Hospital during the years 1941 through 1946. Although the pathologists who had done these autopsies had not observed them, typical pigmented casts as well as toxic changes in the tubules were found in the kidneys of 2 patients, indicating that these hemolytic reactions were being overlooked by pathologists as well as by clinicians.

Next, the free hemoglobin of the plasma was determined by the method of Flink in a series of hospital patients before and after the intravenous administration of normal saline, 5 per cent glucose in saline, and 10 per cent glucose in distilled water, as well as after the use of surgical diathermy without irrigation in neurosurgical patients, and after a variety of open operations involving neither diathermy, intravenous solutions, nor irrigation of the urinary tract. Forty-two cases were studied in all (table 2). The free hemoglobin averaged 5.0 mg.

per cc of plasma before treatment or operation, and 5.7 mg. per cent immediately afterward. There were no striking variations from these averages, which probably represent the very slight hemolysis which is likely to attend the collection and transportation of blood, no matter how carefully done.

Similar measurements were then made in a series of 106 consecutive transurethral resections in which sterile water was the irrigating fluid. Most of these were done at the University Hospital by the resident staff (table 3, *A*). The results show convincing evidence of hemolysis, although there was no level which could be construed as dangerous according to the literature. The free plasma hemoglobin averaged 3.08 mg. per cent before and 45.4 after operation. This is a 15 fold increase and appears to be significant, since no such variation was observed either in the controls or in the patients in whom a non-hemolytic irrigating solution was used. It is to be noted that there were no severe nor fatal reactions in the group, although 8 patients developed mild oliguria, elevation of the urea nitrogen, and disproportionate anemia; mild jaundice was seen in 3 of them. Their postoperative plasma hemoglobins averaged 81 mg. per cent, further supporting the view that hemolysis during transurethral resection is important.

TREATMENT

Keeping the patient alive with kidneys severely damaged as the result of hemoglobinuria taxes clinical judgment. Since Flink and others have seen signs of regeneration in the renal tubules damaged by hemoglobinemia within 5 to 7 days after injury, one must strive to keep the patient alive as long as possible. It is extraordinarily difficult to avoid being meddlesome, especially in the matter of fluids, and one must strive to maintain fluid balance without overloading the circulation to the point of pulmonary edema. Oxygen therapy seems indicated in the initial stages, since vasospasm probably damages the tubules by reducing their supply of oxygen (Maegraith, Havard and Parsons). Whether the use of the tent or mask can increase the oxygen saturation of the blood sufficiently to be of assistance is very doubtful, but increasing the supply of oxygen available to the lungs can do no harm. It is possible that the intravenous administration of oxygen might be more helpful.

Flink has observed that the forcing of fluids immediately after hemolysis hastens the disappearance of free hemoglobin from the plasma in experimental animals, but hemolysis has occurred during transurethral resection while the patient was receiving a continuous intravenous drip of 10 per cent glucose. The injudicious forcing of fluid in an old man with oliguria is more likely to lead to cardiac failure and pulmonary edema than to an improvement of renal function.

The most accurate method of following fluid balance in oliguric patients consists of daily accurate weighing of the patient, and of giving no more fluid than is required to keep the weight constant (or to allow it to fall slowly). Unfortunately, conditions in private hospitals in this area are not such as to permit the use of this extremely valuable method.

The intravenous administration of isotonic sodium sulphate has been advised by Necheles and Olsen on the basis of their experience with dogs rendered anuric by experimental burns (shown by Shen, Ham, and Fleming and by other to be due to hemoglobinemia) where its use has been followed by diuresis in each case, but the writers have not tried it. Their animals were killed at the end of the experiments, so that it is not known whether the diuresis produced by this agent under highly artificial experimental conditions (cannulated ureters) would occur or be useful clinically. The wisdom of using any sodium salt in the presence of oliguria is doubtful.

The acidosis which usually accompanies uremia must be controlled by the administration of alkalis without overloading the patient with sodium or producing an alkalosis which may impair the renal function. As was pointed out in the review of the literature, it seems unlikely that therapy with alkali is of any value in preventing or relieving the oliguria by enhancing the solubility of the hemoglobin or acid hematin in the tubules. It did no good in our fatal case, nor has it seemed to be of value in patients transfused with incompatible blood.

The inevitable anorexia may require tube feeding and the administration of parenteral vitamins. In the early stages nasal suction may be needed for persistent nausea and vomiting. Proteins may require parenteral replacement, and the anemia resulting from blood loss and hemolysis may demand transfusion. Since a hemolytic reaction has already occurred, matching of the blood should be painstaking.

While waste products are piling up in the blood as a result of the oliguria or anuria, one may perhaps gain time for repair of the renal damage and may lessen the toxemia attendant upon the uremia by employing peritoneal lavage, a subject recently reviewed by Fine, Frank and Seligman. The writer has had experience with this procedure in 2 cases in addition to the one already mentioned: one a severe reaction from a transfusion of incompatible blood, and the other an intoxication from sulfathiazole. In both these cases however, the lavage, after removing large quantities of nitrogenous substances from the blood, became ineffective after 3 days because of "walling off" around the inflow and outflow tubes, although it undoubtedly contributed greatly to the patients' recovery. Whether peritoneal reaction can be prevented by changes in the composition of the irrigating fluid (Hartman's solution with 5 per cent glucose added), or whether it is due primarily to bacterial action, remains to be determined. It can be seen that, even with these limitations, peritoneal lavage may turn the tide in the patient's favor in some circumstances, but it must be pointed out that the method carries so much danger of fatal peritonitis that it should not be used unless the prognosis is apparently hopeless. The artificial kidney of Kolff may prove useful in these cases.

It is obvious that the solution to the problem lies in the prevention of hemolysis during transurethral resection rather than in the treatment of the ensuing hemoglobinuria and its effects. One move in this direction consists in using the irrigating fluid at the lowest possible pressure, but it is unlikely that one can see clearly with a pressure low enough to prevent the entrance of fluid into the circulation if prostatic veins are opened widely.

spasm of its vessels, by a direct toxic action upon the tubular epithelium, and by the production of pigmented casts which plug the nephron.

Intravesical and intravascular hemolysis may be produced during transurethral prostatic resection by the water used as an irrigating fluid.

Hemoglobinemia probably does not harm the kidney unless the hemolysis is very severe, or unless the kidney is simultaneously damaged by vasospasm from excessive blood loss or by surgical shock, or by the transportation of virulent bacteria from the prostate to the kidney by the irrigating fluid.

A hemolytic reaction may be recognized at once by measuring the free hemoglobin in the plasma at the end of the operation. This is recommended as a routine procedure with transurethral resection if water is used for irrigation. The reaction itself is characterized by chills, nausea, oliguria, a rising urea nitrogen, a mild jaundice, by an anemia out of proportion to the amount of blood actually lost during and after operation, and at times by a late rise in blood pressure. The hemoglobinuria is masked by the usual postoperative hematuria.

The forcing of fluids during and immediately after operation may aid in excreting the hemoglobin with less damage to the kidneys, but after oliguria has appeared, one must be very cautious in administering fluids. Otherwise, treatment consists in trying to keep the patient alive until sufficient time has elapsed to permit recovery of the damaged renal epithelium. Peritoneal lavage may be of some value in achieving this end.

The hemolytic reaction can be prevented by using an isotonic solution of a poor electrolyte such as 4 per cent glucose, as an irrigating fluid during transurethral resection of the prostate.

A fatal reaction is reported in a case in which sterile water was the irrigating agent. Anorexia, hemoglobinemia, anemia, jaundice, uremia, and hypertension occurred. Peritoneal lavage brought about a remarkable reduction in the urea nitrogen without a diuresis, but death occurred from pulmonary edema.

Clinical studies have shown that water, when used as an irrigating solution during transurethral resection, does produce hemolysis which may be severe enough to cause uremia, and that hemolysis does not occur when isotonic glucose is used. Evidence is presented of the extensive absorption of glucose during operation.

The use of an isotonic solution for irrigation during transurethral resection has resulted in a striking reduction of morbidity and mortality.

Grateful acknowledgment is hereby made to my colleagues whose work made this paper possible: Dr. G. B. Eaves, resident in urology at the University Hospital; and to Dr. David Anderson, a volunteer in urology; to Drs. E. A. Webb and B. A. Smith, Jr., my associates; and to Dr. Gerald Evans, Director of the Laboratories at the University Hospital.

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THE CAUSES OF DEATH FOLLOWING TRANSURETHRAL RESECTION OF THE PROSTATE[1]

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According to a recent national census, the likelihood is about 1 in 300 that a man will die during any 3 week period in his seventieth year. (Crowe, in a personal communication.) In terms of mortality this means a rate of about 0.3 per cent. Such a death rate then should be our goal in the surgical relief of prostatic obstruction. That it can ever be reached is questionable. Nevertheless, it is generally agreed that transurethral resection of the prostate, when properly executed, more nearly approaches this figure than any other form of prostatic surgery. In centers where there has been considerable experience with prostatic resection, the mortality rates are now approaching 1 per cent. At the Mayo Clinic, for example, during the years 1935 through 1945 approximately 12,000 resections were performed with a death rate of 1.3 per cent. (Emmett, in a personal communication.)

Many of the factors which have made it possible to reduce the surgical risk in prostatic resection are well recognized. It is not within the scope of this paper to review them again. We are presenting a study of 16 fatalities following transurethral resection, because we believe the analysis discloses possibilities of further reducing resection mortality by measures which as yet have not received sufficient attention. In this series the cause of death appears to have been accurately established by autopsy data which were obtained in a high percentage (81 per cent) of the cases. The importance of deriving statistics based on autopsy material is apparent when one realizes that even in our best medical centers the correlation between clinical and autopsy diagnosis in the aged is low. This series of cases also serves to emphasize the importance of the oliguria syndrome in prostatic resection.

The first transurethral resection in Mary Hitchcock Memorial Hospital took place in 1933. Up until May 31, 1947, there were 561 resections (table 1) on approximately 535 patients. Sixteen patients died, giving a mortality rate of 2.9 per cent. Of these 16 deaths, 13 came to autopsy.

The following is a chronological presentation of each case with the clinical or autopsy diagnosis:

Case 1. H. T., aged 75, death December 14, 1933. Anatomic diagnosis: 1) Recent (3 day) transurethral resection of prostate gland for adenocarcinoma with extension to left seminal vesicle and metastasis to regional lymph nodes; 2) recent (3 day) suprapubic cystostomy for hemorrhage from operative site;

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., July 1, 1947.

3) shock (clinical); 4) bronchopneumonia; 5) *suppurative pyelonephritis*, right; 6) hydroureter and hydronephrosis, right, infected; 7) cellulitis of forearm; 8) ulcerative proctitis.

Case 2. F. H., aged 72, death February 22, 1935. Anatomic diagnosis: 1) Recent (19 day) transurethral resection of prostate gland for adenofibroma; 2) thrombophlebitis of iliac vein, left; 3) multiple emboli of pulmonary arteries; 4) gangrene of scrotum; 5) hypertrophy of heart (540 gm./350 gm. normal); hypertension (clinical); 6) ancient infarct of myocardium; 7) ancient infarct of basal ganglia, left; 8) ancient infarct of spleen; 9) diverticulum of bladder with diverticulitis; 10) nephrolithiasis, left; 11) cholelithiasis; 12) inguinal hernia bilateral.

Case 3. E. L., aged 77, death May 21, 1935. Anatomic diagnosis: 1) Recent (4 day) transurethral resection of prostate gland for adenocarcinoma with metastasis to regional lymph nodes; 2) recent septic infarct of spleen and kidney (gram negative bacilli); 3) bronchopneumonia.

TABLE 1

Total number of resections (1933 through May 1947)	561
Total number of deaths	16
Mortality	2.9%
Autopsies	13
Correlation of clinical with autopsy diagnosis	46%
Average age	69.5
Prostatic lesion	
Adenofibroma	10
Adenocarcinoma	6

Case 4. E. L., aged 65, death April 19, 1936. Anatomic diagnosis: 1) Recent (2 day) transurethral resection of prostate gland for adenocarcinoma with carcinomatosis, and litholapaxy for calculus in bladder; 2) acute necrosis of adrenal glands; 3) acute adrenal insufficiency (clinical), suspected; 4) multiple diverticula of bladder.

Case 5. E. D., aged 66, death December 19, 1937. Anatomic diagnosis: 1) Recent (15 day) transurethral resection of prostate gland for adenofibroma; 2) perforation of bladder with perivesical abscess and peritonitis; 3) septicemia (E. coli), clinical; 4) suppurative pyelonephritis, bilateral; 5) bronchopneumonia; 6) healed infarct of myocardium.

Case 6. J. S., aged 65, death June 30, 1938. Anatomic diagnosis: 1) Recent (6 day) transurethral resection of prostate gland for adenofibroma with probable perforation of bladder neck; 2) retroperitoneal pelvic abscess; 3) peritonitis; 4) septicemia (Streptococcus hemolyticus), clinical; 5) atelectasis of lung, partial, bilateral.

Case 7. F. L., aged 67, death June 26, 1939. Autopsy refused. Clinical diagnosis: 1) Recent (24 day) transurethral resection of prostate gland for adenocarcinoma with questionable perforation of urethra; 2) recent (4 day) incision and drainage of periurethral cellulitis and extravasation; 3) septicemia (hemolytic E. coli); 4) epididymitis, left.

Case 8. T. D., aged 64, death February 29, 1940. Autopsy refused. Clinical diagnosis: 1) Recent (20 day) transurethral resection of prostate gland for adenofibroma; 2) septicemia (Streptococcus hemolyticus); 3) urosepsis (Streptococcus hemolyticus).

Case 9. R. B., aged 72, death September 15, 1940. Anatomic diagnosis (autopsy limited to abdominal incision): 1) Recent (4 day) transurethral resection of prostate gland for adenocarcinoma with metastasis; 2) recent (4 day) suprapubic cystostomy for hemorrhage from operative site; 3) oliguria and uremia, clinical; 4) bronchopneumonia, suspected; 5) cirrhosis of liver; 6) cholelithiasis; 7) diverticulum of duodenum; 8) diverticulosis of colon; 9) healed duodenal ulcer.

Case 10. F. L., aged 69, death August 19, 1942. Autopsy refused. Clinical diagnosis: 1) Recent (9 day) transurethral resection of prostate gland for adenofibroma of prostate with perforation of the vesical neck; 2) recent (8 day) drainage of prevesical space; 3) oliguria and uremia, clinical.

Case 11. G. S., aged 70, death August 2, 1944. Anatomic diagnosis: 1) Recent (2 day) transurethral resection of prostate gland and suprapubic cystostomy for adenofibroma; 2) thrombosis of pelvic and femoral veins; 3) embolism of main pulmonary artery; 4) edema of lungs (right, 750 gm.; left, 625 gm.); 5) hemorrhage into bladder (1,000 cc); 6) obesity (due to excess food?); 7) atelectasis of lungs, partial; 8) hypertrophy of heart (600 gm./450 gm. normal); hypertension (clinical).

Case 12. D. D., aged 66, death October 17, 1944. Anatomic diagnosis: 1) Recent (22 day) hemorrhage following rapid decompression of chronically distended bladder; 2) recent (18 day) transurethral evacuation of clots from bladder, electrocoagulation of bleeding vessels, and resection of prostate gland for adenofibroma; 3) arteriosclerosis of coronary arteries (grade 3) with recent (22 day) infarct of left ventricle; 4) hydronephrosis with atrophy, bilateral; 5) uremia and anemia, clinical; 6) hypertrophy of heart (550 gm./375 gm. normal); hypertension (clinical).

Case 13. J. N., aged 75, death October 23, 1944. Anatomic diagnosis: 1) Recent (9 day) suprapubic cystolithotomy and cystostomy; 2) recent (3 day) transurethral resection of prostate gland for adenofibroma; 3) embolism of main pulmonary artery (site of origin undetermined); 4) nephrolithiasis, right; 5) encrustation cystitis; 6) adenoma of thyroid; 7) healed duodenal ulcer; 8) diverticulum of duodenum.

Case 14. E. C., aged 74, death February 2, 1945. Anatomic diagnosis: 1) Recent (10 day) transurethral resection of prostate gland for adenocarcinoma; 2) recent (10 day) suprapubic cystostomy for hemorrhage from the operative site and perforation of bladder neck; 3) "hemoglobin" nephrosis; 4) oliguria and uremia, clinical; 5) pyelonephritis, acute; 6) anasarca; 7) recurrent acute pancreatitis; 8) subactue cholecystitis; 9) acute necrosis of liver.

3) shock (clinical); 4) bronchopneumonia; 5) suppurative pyelonephritis, right; 6) hydroureter and hydronephrosis, right, infected; 7) cellulitis of forearm; 8) ulcerative proctitis.

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Case 7. F. L., aged 67, death June 26, 1939. Autopsy refused. Clinical diagnosis: 1) Recent (24 day) transurethral resection of prostate gland for adenocarcinoma with questionable perforation of urethra; 2) recent (4 day)

Predisposing factors such as inadequate mobilization and obesity appeared to play an important role in the formation of thrombi in the leg veins.

The patient who died of coronary artery disease probably suffered his major myocardial infarct at the time he had massive hemorrhage from the bladder and prostatic surface. Despite the fact that this patient had been in chronic urinary retention, he was subjected to a rapid decompression of the bladder before being sent into the hospital. This very likely brought on the hemorrhage which was followed by transient hypotension and myocardial infarction. It was deemed advisable at the time of the clot evacuation to resect a small amount of prostatic tissue in order to get at the bleeding vessels more easily with the electrocautery unit. A complete resection was not carried out.

The post-resection oliguria syndrome has been the subject of much discussion recently. As an entity, this type of oliguria appears to be distinct from the occasional postoperative oliguira which follows exsanguination and prolonged hypotension. The 3 patients who fell into this category have already been described in detail by the authors. Each of these patients had excessive bleeding and prolonged attempts at hemostasis. Two had perforations of the vesical neck. In only 1 patient did the blood pressure ever drop to a so-called "shock level" and this probably lasted only 5 minutes. In 1 patient renal findings characteristic of "lower nephron nephrosis" were disclosed. There were areas of necrosis throughout the parenchyma and several tubules contained blood pigment casts. Creevy has presented an excellent analysis of a well-documented case that had a hemolytic reaction during a resection. This patient developed oliguria and died in uremia.

The exact mechanism of the oliguria syndrome is not entirely understood at the present time. It is likely, however, that tissue damage, whether it be hemolysis of red blood cells or destruction of the periprostatic and perivesical tissues, leads to a specific renal response characterized by lowered urinary output and uremia. The tissue damage is probably brought about by hypotonic irrigating solution (sterile tap water) which hemolyzes the blood when it enters the circulation by the prostatic veins or damages the periprostatic tissues when perforation occurs.

The oliguria syndrome can probably be prevented by the use of isotonic solutions. Such irrigating media as physiologic saline and 5 per cent dextrose solutions, however, have definite limitations. Indeed, it is probable that nothing will completely supplant plain water because of its availability and technical advantages. Resectionists who continue to use water must realize that dangerous levels of free hemoglobin in the plasma may be produced by the hemolysis mechanism. In order to prevent excessive hemoglobinemia, the height of the column of irrigating solution should be kept at the lowest possible level and prolonged attempts at hemostasis should be avoided when venous bleeding is encountered.

Hemorrhage and shock accounted for death in 1 patient despite suprapubic cystostomy, prostatic packing and transfusions.

The death from agranulocytosis was probably due to insufficient care in following the white blood cell count while the patient was receiving sulfadiazine. The agranulocytosis occurred with only a gram of sulfadiazine daily.

The patient suffering from acute necrosis of the adrenal glands died 48 hours after resection in what appeared to be an acute adrenal insufficiency state. This condition was unrecognized before death.

SUMMARY

An analysis of 16 fatalities following transurethral resection of the prostate gland has been presented. It is evident that more than half of these deaths were due to factors over which the resectionist had direct control. In order to reduce future prostatic resection mortality, the technique of resection must be better understood and applied. The use of prophylactic antibiotics and chemotherapy before, during, and after resection should materially reduce the incidence of death due to sepsis. Early mobilization of patients and the use of active leg exercises for bed patients would appear to be our most effective means of lowering the number of fatal pulmonary emboli due to thrombosis of the leg veins. The use of isotonic irrigating solution or the judicious use of sterile water during resection should reduce the incidence of the oliguria syndrome.

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DISCUSSION

DR. GERSHOM J. THOMPSON (Rochester, Minn.): This research by Dr. Creevy and his co-workers is the finest which has been done in the field of transurethral surgery in recent years. Undoubtedly, it will stimulate further efforts and everyone will be interested in using these methods to promote safer transurethral resection.

One of the fellows in the Mayo Foundation, Dr. C. L. Biorn, and my associate, Dr. L. F. Greene, have studied a fairly large number of cases and I shall briefly mention some of their findings. A comparatively simple method of determining the presence of abnormal amounts of hemoglobin in the plasma is the gross comparison of specimens of blood drawn from the vein immediately preoperatively, and immediately postoperatively and at regular intervals for 10 to 12 hours. To prevent coagulation of the samples, and hence injury of the cells, the plunger of the syringe and the centrifuge tubes are dusted with powdered heparin. The sample is immediately centrifuged and the supernatant plasma examined. Until a level of hemoglobin well above 5 mg. per cent is reached, the plasma remains straw colored. When the concentration reaches about 25 mg. per cent, the plasma takes on an orange hue and above this level, it becomes light pink and finally a deep red depending upon the concentration of hemoglobin. Accurate quantitative measurements can be made by treating the plasma with certain chemicals and examining the mixture by spectrophotometric methods. This kodachrome slide portrays 3 specimens of blood drawn immediately pre- and postoperatively and 13 hours postoperatively. It can be seen that the second sample of plasma is deep red in color. By quantitative examination, this specimen was found to contain 792 mg. per cent of hemoglobin. At the end of 13 hours, the color of the plasma has changed to orange and quantitative analysis shows a reduction to 47 mg. per cent. This second kodachrome slide shows 6 samples of blood collected immediately preoperatively, 1 minute, 5 hours, 10 hours, 20 hours and 40 hours postoperatively. The color, as you can see, changes during this time postoperatively from red to pink and finally back to the normal color. The accurate quantitative estimates dropped from 588 mg. per cent successively to 208 mg., 66 mg., 24 mg. and finally 5 mg. per cent which can be regarded as nearly normal since any sample, no matter how carefully drawn, will contain minute amounts of hemoglobin.

It can be graphically seen that hemoglobin is rather rapidly eliminated from the plasma probably in large part by the reticulo-endothelial cells. The concentration of hemoglobin in the plasma at which noticeably harmful effect on the kidneys will occur, has to my knowledge not yet been established in humans. It would probably vary in different patients and no certain level would apply at which measurable renal injury would occur in all cases.

In a series of 100 cases, all operated upon with the Thompson resectoscope, 55 per cent showed a postoperative concentration of hemoglobin above 25 mg. per cent (slide). None of these patients suffered with appreciable oliguria though several had anorexia, nausea and 2 had slight hemolytic jaundice. Five patients whose plasma hemoglobin varied from 516 mg. per cent to as high as 1,040 mg. per cent, suffered no oliguria as evidenced by an output of urine which averaged 2,000 cc or more daily on the second, third and fourth postoperative days and a continued high output beyond that time. Measurement of the output on the first day was precluded by continuous and intermittent irrigations.

In Dr. Creevy's series of cases, the highest plasma hemoglobin was 490 mg. per cent with the exception of his fatal case in which it was undoubtedly well above that level since he states that the plasma was deep red in color on the evening of the day of operation. In my patient, wherein the level was 1040 mg. per cent immediately postoperatively, there was no oliguria but he did have anorexia for 24 hours and developed a slight jaundice. It seems likely that other factors in addition to the presence of hemoblogin in the plasma are important in the development of severe renal injury.

The exact mechanism of the appearance of hemoglobin in the plasma is none too clear. Solutions of saline of 0.9 per cent are isotonic and in studying red cell fragility in the test tube, one must reduce the tonicity below 0.42 per cent before the cells rupture. If plasma behaves similarly, given an individual with a total blood volume of 6 liters, he would have to lose at least a liter of blood and absorb 2½ liters of water before theoretically a 50 per cent dilution would occur and hemolysis could take place. In his experiments with 4 per cent glucose, Dr. Creevy noted 1 case whose blood sugar rose to more than 1,000 mg. per cent. This would mean in a man with a 6 liter blood volume, the entrance of 1½ liters of irrigating solution, which is below the theoretical level necessary to produce intravascular hemolysis. However, it must be pointed out that rapid injection of water into an open prostatic venous sinus might possibly hemolyze a certain amount of blood in the immediately adjacent veins and in this manner, repeated rapid increments of water would account for intravascular hemolysis. *Intravesical* hemolysis and the forcing of this solution of hemoglobin from the bladder into the veins is probably the more important mechanism of the production of high plasma levels.

I believe it should be pointed out that the use of a solution which prevents hemolysis does, in fact, increase technical difficulty by making vision less clear, especially when bleeding is profuse. Using the Thompson resectoscope, one can employ normal saline solution for irrigation since diffusion of the cutting current is not a factor. In two instances, we have had to switch to water because the unhemolyzed blood interfered with vision and reduced the accuracy of performance of the operation. I believe other urologists, especially those less skilled than Dr. Creevy, will encounter difficulty in using nonhemolyzing solutions.

It seems to me that this splendid work of Creevy and his assistants will stimulate search for other solutions. Effort need not be confined to those which prevent hemolysis in the bladder. There must be some safe solution which will destroy the hemoglobin immediately after its release from the exploded red blood corpuscle before it is forced into the open venous sinuses. Such a solution would possess all the advantage of glucose or glycine solutions and yet not add to the technical difficulty by interfering with vision. Also, if one grants that local intravascular hemolysis occurs by rapid injection of water into the large veins immediately above the prostate gland, this substance in solution should destroy and thus render the resulting released hemoglobin innocuous.

In closing, I wish to call attention to one other point in Dr. Creevy's paper. He stated that his pathologist, Dr. Bell, carefully reviewed the sections of the kidneys of 6 fatal cases of oliguria following transurethral resection and found typical casts and toxic changes in the tubules in only 2 cases. Our pathologists at the Mayo Clinic have likewise found these changes in the very small minority of cases. It would seem to me probable that hemoglobinuria and vascular spasm are only a part of the answer to the problem of oliguria and renal insufficiency following transurethral resection. We are indebted to Dr. Creevy for a splendid start on its complete solution.

DR. HENRY S. BROWNE (Tulsa, Okla.): On January 16, 1946, I did a transurethral resection on a man, aged 74, removing 37 grams of tissue. Bleeding was moderate but controlled readily. Three hours later he had a sudden severe hemorrhage with blood gushing out around the catheter. He was returned to the operating room and the bleeding controlled by fulguration. The prothrombin estimation at this time showed a clotting time 50 per cent of normal. Although he was given 1,000 cc of blood and 500 cc of plasma, he never recovered from shock and died 6 hours later. Since that time I have had a prothrombin estimation done in every case before operation and if the clotting time is below 70 per cent of normal, the patient is given vitamin K twice daily by needle and calcium gluconate by mouth. In a few days this will bring the clotting time to above 70 per cent, and since following this procedure, I have noted a definite and marked decrease in bleeding both at operation and after. I believe, therefore, strongly in having the clotting time well up toward normal before doing a resection. Transfusions of course are necessary. I am glad to hear Dr. McLaughlin advise less fulguration of venous bleeding points, as they seem to keep on bleeding no matter how much you spark them, although I have never had to return a patient to surgery on account of postoperative venous bleeding. Following a resection there is an open surgical wound in a closed sac, bathed in infected urine, for no matter how aseptic we are, the catheter, being a foreign body, will cause infection to be introduced into the prostatic cavity by direct extension. It is a wonder, therefore, that we do not have more trouble from infection than we do, and like the essayists, the majority of my deaths have been due to this cause. These old men can stand 1 or maybe 2 chills and high temperature, but after that they usually lose interest in life, refuse to eat and eventually die. I have had 4 patients in whom the temperature reached 107° following a chill. In these cases the temperature never went above normal afterward and they all recovered. I wonder if the high temperature did not kill the infection but am not recommending this method of combating it. By giving 2 gm. of a sulfonamide daily for 2 days before operation, and penicillin in large doses if the temperature goes above 102° afterward, my troubles with infection have been greatly reduced. Transfusions in these cases also are a great help. In dealing with men of the prostatic age, no matter how careful one is, there will occasionally be a death from some cardiovascular disease, and although the blood chemistry may be normal and the urine output excellent before operation, an occasional patient may develop uremia and pass away. This may be due to the oliguria syndrome so well described by Creevy and the other essayist. I thoroughly enjoyed Dr. McLaughlin's paper and wish to especially compliment him on his high percentage of autopsies and his concise and detailed case reports.

DR. WILLIAM L. MCLAUGHLIN (Hanover, N. H.): I would like to say a word about the possibility that hemoglobinemia may not be the entire answer in the problem of post resection oliguria. It has been shown experimentally that certain breakdown products of hemoglobin and combinations of these hemoglobin derivatives with plasma proteins are more toxic than hemoglobin alone. Two of the patients reported in our paper had evidence of liver disease. These patients may have had abnormal plasma protein patterns. The combination of hemoglobin or a hemoglobin derivative with one of their plasma proteins may have created a compound more toxic to the kidney than free hemoglobin itself.

Dr. Browne's suggestion about the use of vitamin K preoperatively to improve the blood clotting mechanism is most interesting and helpful.

DR. C. D. CREEVY (closing): Time did not permit dealing with a good many aspects of this subject. All I can say is that since I have been using glucose during the last year, my life has been very considerably simplified. I used to be perfectly sure that, if I had a long, bloody resection, I would come back the next day and find the patient sick. I do a long, bloody resection now, often without transfusion, and come back next day to find the patient eating his breakfast.

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ANURIA: ITS TREATMENT BY PERITONEAL DIALYSIS[1]

WM. NILES WISHARD, Jr., H. G. HAMER and HENRY O. MERTZ

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Anuria is always a medical challenge which too often terminates in fatal uremia. Its underlying cause is legion. Renal failure may be reversible or irreversible, but when anuria ensues the therapeutic difficulty lies in predetermination of this factor. It has been pointed out by others[2, 3, 4, 5, 12, 13, 14] that acute renal failure with reversible changes is frequently fatal because of accumulation of substances normally excreted, and that artificial removal of these products should lower the mortality. Fine et. al.[3, 4, 5] have defined the reversible changes as due to transfusion reaction, sulfonamide toxicity, massive trauma, toxemia of pregnancy, mercury poisoning, and acute glomerulonephritis; and state that uremia is fatal becaues the renal lesion requires more time for repair than the lethal effects of uremia will permit. This could be avoided if, during the repair period, some extrarenal excretory route could be substituted. Abbott and Shea[6] have ascribed uremic death to accumulation of toxic products, changes in osmotic pressure of the body fluid, dehydration or overhydration, and acid base imbalance. These toxic substances are not yet identified, although Gamo[7] believed they contained oxyproteic acid, and Cristol thought polypeptids. They are dialyzable and contain nitrogen.[7]

Various extrarenal excretory substitutes have been explored. In 1914 Abel, Rowntree and Turner[2] used celloidin tubes for dialysis. Putnam[8] in 1923 tried the peritoneum as a dialyzing membrane. Rhoades[9] in 1938 used peritoneal injection of fluids, and Ochsner[5] has recommended gastric lavage, 20 litres daily. Kolf and Berg[10] in 1944 used a revolving drum around which was wound a 40-

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

Invaluable assistance was given by Drs. Banks and Hoyt (pathology), Dr. J. A. MacDonald (medicine), Drs. Gatch and Owen (surgery), Drs. Smith and Sutton (residents), and Mr. Spurling Clark (pharmacist) and Nelma McClay (chemist). The expense of laboratory work was borne by the administration. Self-effacing, careful nursing was a comfort to the patient and a credit to the profession.

[2] Goodyear, W. E. and Beard, D. E.: The successful treatment of acute renal failure by peritoneal irrigation. J. A. M. A., 133: 1208, 1947.

[3] Frank, H. A., Seligman, A. M. and Fine, J.: Treatment of uremia after acute renal failure by peritoneal irrigation. J. A. M. A., 130: 703, 1946.

[4] Seligman, A. M., Frank, H. A. and Fine, J.: The treatment of experimental uremia by peritoneal irrigation. J. Clin. Invest., 25: 211, 1946.

[5] Fine, J., Frank, H. A. and Seligman, A. M.: The treatment of acute renal failure by peritoneal irrigation. Ann. Surg., 124: 857, 1946.

[6] Abbott, W. E. and Shea, P.: Treatment of temporary renal insufficiency by peritoneal lavage. Am. J. Med. Sc., 211: 312, 1946.

[7] Wear, J. B., Sisk, I. R. and Trinkle, A. J.: Peritoneal lavage in the treatment of uremia. J. Urol., 39: 53, 1938.

[8] Putnam, T. J.: The living peritoneum as a dialyzing membrane. Am. J. Physiol., 63: 548, 1923.

[9] Rhoads, J. E.: Peritoneal lavage in the treatment of renal insufficiency. Am. J. Med. Sc., 196: 642, 1938.

[10] Kolf, W. J. and Berk, H. T. J.: The artificial kidney; A dialyzer with a great area. Acta. Med. Scandinav., 117: 121, 1944.

yard 23 mm. cellophane tube connected to the arterial supply at one end and the venous outlet at the other. The drum rotated in a tank of solution containing NaCl 0.06 per cent, KCl 0.04 per cent, $NaHCO_3$ 0.2 per cent and 1.5 per cent glucose for 10 to 14 hours. The patient was heparinized with 1200 mg. of heparin. Eleven patients have been thus relieved out of 27 trials. Bliss[11] in 1932 found that nephrectomized dogs, which usually die in 3 days, could be kept alive for 16 days by intermittent injection of balanced salts solution into the peritoneum for ten minutes and then drawn off. To Wear, Sisk and Trinkle[7] goes the credit for the first use of peritoneal dialysis on a human being with survival. They used buffered Locke-Ringer's solution. They pointed out the importance of not removing salt, calcium and glucose in the course of dialysis. Their paper gives an excellent bibliography of the development of peritoneal dialysis. Abbott and Shea[6] commented in March 1946 that previous methods of peritoneal lavage failed because water and electrolyte balance were not considered and gave the criteria of proper solution as permitting a maximum diffusion of waste into it, the property of not altering the electrolyte pattern of extracellular fluid, having the desired tonicity and affording nutrition, and keeping protein catabolism at a minimum. Gatch (in a personal communication) has called attention to the fact that the peritoneum retains the power to filter nitrogenous wastes from the blood which is possessed by the primitive creatures from which man has evolved, the earliest form of glomerules having been a capsule of peritoneum.

Abbott and Shea[6] writing in 1946 state that peritoneal lavage has been used on 13 patients, Wear's[7] case alone surviving. Rhoads[9] classified these cases in 1938:

Ganter (1923), 1 case, chronic nephritis, died.
Heuser and Werder (1927), 3 cases, cause unstated, unsuccessful.
Balaza and Rosenak (1934), 2 cases, bichloride poisoning, died.
Wear and Sisk (1938), 5 cases, carcinoma of bladder (2), died; bilateral hydronephrosis (2), died; reflex anuria with obstruction (1), lived.
Rhoads, 2 cases, chronic nephritis, died.

To which may be added the following more recent reports:

Fine et al. (1946), 4 cases, sulfonamid anuria (1), recovered; transfusion reaction (2), died; carcinoma of cervix (1), died.
McGraw (1946), 1 case, nephritis and nephrosis nonprotein nitrogen lowered.
Flocks (personal communication) (1946), 2 cases, nephritis, died.
Creevy (personal communication) (1946), 3 cases, transfusion reaction (1), recovered; hemolysis following resection (1), died; sulfonamid anuria (1), recovered.

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[11] Bliss, S., Kastler, A. O. and Nadler, S. B.: Peritoneal lavage, effective elimination of nitrogenous wastes in the absence of kidney function. Proc. Soc. Exp. Biol. and Med., 29: 1078, 1932.

[12] Smith, B. H. and Eaves, G. B.: Temporary renal insufficiency. Staff Meeting Bulletin, Hospital of the University of Minnesota., 18: 191, 1947.

[13] Muirhead, E. E., Small, A. B. and McBride, R. B.: Peritoneal irrigation for uremia following incompatible blood transfusion; Report of a case. Arch. Surg., 54: 374, 1947.

[14] Creevy, C. D. and Webb, E. A.: A Fatal hemolytic reaction following transurethral resection of the prostate gland. Surgery, 21: 56, 1947.

Smith and Eaves (1946), 2 cases, sulfonamide anuria (1), died; hemolysis following resection (1) recovered.
Schaaf (personal communication) (1947), 1 case, sulfonamide anuria (1), recovered.
Muirhead et al. (1947), 1 case, transfusion reaction (1), recovered.
Goodyear et al. (1947), 1 case, transfusion reaction (1), recovered.
Authors (1947), 1 case, nephrosclerosis and sulfonamid anuria (1), died.

This brings the total number to 29 with 9 survivals some of which subsequently showed clinical pathologic evidences of relative renal insufficiency. Undoubtedly the method has been used more often without publication of any report. Kolf recently mentioned the use of lavage at the meeting of the Chicago Urological Society, and O'Conor has also made use of the method.

In 1946 Fine et al.[3, 4, 5] found that peritoneal irrigation would remove crystalloids from the blood with efficiency adequate to substitute for renal function and sustain life many days. They used mammalian Tyrode's solution (20 to 30 litres daily), designed to avoid plasma depletion of electrolytes, glucose to avoid acidosis, and penicillin and sodium sulfadiazine to prevent infection, and heparin to inhibit fibrin deposition. They[5] emphasize that the peritoneum is a good dialyzer, permeable to water and crystalloids, and removes the diffusable substances from the plasma and extracellular fluids. Proper adjustment of the irrigating solution prevents subnormal depletion of plasma concentration and protects the chemical structure of extracellular fluids. Experimentally they determined that peritoneal irrigation would provide 40 per cent to 75 per cent of normal kidney function (terms of urea clearance). Tyrode's solution per litre contains the following (anhydrous): $NaCl$ 8 gm., KCl 0.2 gm., $CaCl_2$ 0.1 gm., $MgCl_2$ 0.1 gm., NaH_2PO_4 0.05 gm., $NaHCO_3$ 1. gm., and dextrose 1.5 gm. All the foregoing except $NaHCO_3$ is autoclaved and the latter sterilized separately and added. In addition, the solution contains the sodium salt of heparin (0.25 to .50 mg.). The latter may be omitted if the patient is sensitive. They recommend running the solution through a Mandler filter and water bath at 40° to 45°, and thence to the peritoneal inlet at 40 to 60 cc per minute. They report 4 cases of uremia so treated with one recovery. In discussion of their paper McGraw[5] reported an instance where peritoneal lavage reduced the nonprotein nitrogen from 150 to 95. More recently Goodyear and Beard[2] reported the successful use of peritoneal irrigation for anuria caused by a post nephrectomy transfusion reaction with recovery.

CASE REPORT

The following case report is based entirely upon the method of Fine[5] with the exception that we were unable to use a filter and substituted hot water bottle jackets for the water bath. We were unable to maintain as fast a flow as he suggests because of difficulty (mentioned by others) at times with the outflow. See figure 1.

Mr. A. G. V. (No. 19407) aged 59, a white married man, entered the Methodist Hospital on November 27, 1946, saying that he "did not know why he was there." He had been pretty well until November 20, 1946, when he became first day or two. There was considerable leaking during this time around the outflow. Due to our unfamiliarity with the procedure, sufficient accuracy was not observed in maintaining quantitative records of inflow and outflow. After a day or so no further trouble was experienced with the outflow. On the fourth hospital day (the first day of dialysis) the nonprotein nitrogen was 185 mg. per cent, the creatinine 15 mg. per cent, the blood sulfadiazine level 3 mg. per cent, the blood serum sodium 329 mg. per cent, calcium 9.8 mg. per cent, serum protein 5, and hematocrit 29. The temperature was normal, the blood pressure 110/80, the urine output 0. There was no pain, the abdomen remained distended, and hiccoughs continued. Management consisted of caffeine, morphine, liquid diet, and Watkins enema.

On the fifth hospital day (second of dialysis) the patient complained of gas pains and was mentally confused. The dressings over the kidney incisions (previously dry) were moist, and there was copious leakage from around the exhaust tube. The nonprotein nitrogen rose to 192 mg. per cent, the blood urea clearance was 2 per cent, the serum protein 5.44 (A.G. ratio 1–1), cholesterol 203 mg. per cent, plasma chlorides 5.6 mg. per cent, calcium 9.7 mg. per cent, sulfadiazine level 2.9 mg. per cent, and hematocrit 31. The blood pressure was 140/60, temperature normal, urinary output zero. The fluid intake was maintained by intravenous 5 per cent glucose in distilled water and small amounts of normal saline, totaling 2000 cc. Enemata were continued for distention, as well as a colon tube, with fair results. The peritoneal exhaust fluid contained protein 0.062 mg. per cent, nonprotein nitrogen 61 mg. per cent, and E. coli was found in its culture.

On the sixth hospital day (third of dialysis) the face became edematous, the patient lethargic, and muscular twitching developed. The kidney incisions were quite moist. The nonprotein nitrogen was 165 mg. per cent, creatinine 14 mg. per cent, CO_2 34 vol. per cent, and blood sulfadiazine level 2 mg. per cent. The hematocrit was 30. The intake was 2000 cc intravenously, 5 per cent glucose in distilled water, and 1/6 molar sodium lactate to comabt acidosis. The temperature was 99.4, the blood pressure 120/70. Three cubic centimeters of urine were recovered. The peritoneal outflow was 23 litres. This outflow contained 2 gm. of protein, 77.3 mg. per cent of nonprotein nitrogen (17 gm. total) 88 mg. per cent of urea (19 gm. total) sulfadiazine level 1.03 mg. per cent, and its urea clearance test was 23 per cent.

The seventh hospital day (fourth of dialysis) found the patient's clinical condition unchanged. However, his nonprotein nitrogen was down to 125 mg. per cent, creatinine 11. mg. per cent, and blood sulfadiazine level 1.2 mg. per cent. Plasma chlorides were 599 mg. per cent, CO_3 31 vol. per cent. The fluid intake was 2250 cc, 1500 cc of which was intravenous 1/6 molar sodium lactate for acidosis. The temperature was normal, the blood pressure 170/80. A mild secondary anemia prevailed and the white blood count was 15,100. The peritoneal outflow was 16 litres. It contained E. coli and non-hemolytic streptococci. On this day, the ninth of anuria, 35 cc of urine were excreted, which meagre though it was quantitatively, was a veritable qualitative Niagara. The 16 hour peritoneal outflow contained 0.06 protein (10 gm.), nonprotein nitrogen 47 mg. per cent (7 gm.), 0.8 mg. per cent of sulfadiazine.

On the eighth hospital day (fifth of dialysis) the patient became more alert and took sips of fluid orally. He was nauseated, had distention and severe abdominal pain. Peritonitis was feared so the penicillin in the Tyrode's solution was augmented by giving 100,000 units every 6 hours into the peritoneal intake tube, and penicillin was started intramuscularly and intravenously. Gastric drainage with suction was started. The nonprotein nitrogen fell to 90 mg. per cent, the blood sulfadiazine level to 1 mg. per cent, and the CO_2 rose to 41 vol. per cent. The fluid intake was 2000 cc (1500 cc of which was $\frac{1}{6}$ molar sodium lactate). The temperature was 100, the blood pressure 150/80. Urinalysis showed a large amount of albumin, 25 white blood cells, 10 red blood cells per 4 mm. field, bacteria and no casts. It contained 24 mg. per cent of urea, 7 gm. of NaCl per litre, and 3.1 mg. per cent of sulfadiazine. The peritoneal exhaust totaled 38 litres. A 6 hour 22 litre portion of this contained 0.073 mg. per cent (16. gm. total) protein, nonprotein nitrogen 34.1 mg. per cent, (7 gm. total) and 0.5 mg. per cent sulfadiazine.

Distention, edema and abdominal pain were the order of the ninth hospital day. Penicillin was complemented by streptomycin, 3 gm. daily, which was continued for 1 week in decreasing amounts. Digitalis and aminophylin were given. Sodium lactate and 5 per cent glucose were continued, intake totaling 1500 cc. The peritoneal output was 33.6 litres, (urea clearance 15 per cent, 11 cc, urea 36. mg. per cent). The gastric output 1400 cc and the urinary output 86 cc. The maximum temperature was 99.4, blood pressure 170/80. The nonprotein nitrogen went down to 62 mg. per cent. The blood sulfadiazine level was 0.8 mg. per cent, the blood sugar was 198 mg. per cent, plasma chlorides 673 mg. per cent, protein 5 (1–1 AG ratio). The CO_2 was 42 vol. per cent, the urine urea was 18 mg. per cent, the urine sulfadiazine 1.9 mg. per cent, and urine chlorides 7.5 gm. per litre. The patient was seen this day by Dr. Rubin Flocks, who was visiting in the city, and from him we received valuable information concerning his unpublished experiences with peritoneal irrigation.

The next day (seventh of dialysis) the clinical condition was unaltered. The nonprotein nitrogen was 66 mg. per cent, creatinine 5.9 mg. per cent, urea clearance 0.6 per cent. The urine urea was 72 mg. per cent. The urinary output rose to 295 cc. The peritoneal output was 31 litres, Levine suction 475 cc.

On the eleventh hospital day (eighth of dialysis) the nonprotein nitrogen was 65.7 mg. per cent, CO_2 was 30 vol. per cent. The intake consisted solely of 250 cc of whole blood. The urinary output was 730 cc. The blood pressure and temperature were unaltered. The peritoneal outflow was 34 litres.

On the twelfth day (ninth and last day of dialysis) the patient became overwhelmed with the complexity of his treatment and extracted both peritoneal tubes and the Levine the next day. He failed to notice his indwelling catheter which he left in as an unobtrusive nuisance. His temperature rose to 101, his did not cause protein deficit although no protein was used in the irrigating fluid. Frequent transfusions and some plasma were given.

The procedure was terminated on its ninth day by the sudden removal of tubes by the patient. At the time, however, enough urine was being excreted and the nonprotein nitrogen was low enough (62) so that we hoped the kidneys would be able to handle their load. During the period of dialysis, sulfadiazine disappeared from the blood stream, both via the peritoneal irrigating fluid and the urine. However, upon discontinuing peritoneal lavage, there was an immediate rise of nonprotein nitrogen although the water excreting ability of the kidneys continued to improve. When the chemical evidences of uremia had recurred almost to the level preceding dialysis, they again began to subside and all concerned thought the patient was going to recover. Then, coincidental with removal of the previously continuously anchored catheter, uremia recurred a third and last time terminating in death on the forty-fifth day since onset of anuria. It is possible that longer use of dialysis and more rapid flow would have altered the ultimate outcome. Too much emphasis cannot be placed on the complexity of the method, the need of exhausitive laboratory studies, and of detailed coordinated team work between clinician, nurse, laboratory, pharmacy and house staff. The method is expensive in a private hospital where one has to consider the cost of laboratory studies, preparation and sterilization of fluid, drugs, and private nursing (which is essential). Nevertheless, we commend its use in nonobstructive anuria, particularly if the renal failure may be reversible. Autopsy of our patient showed that the peritoneum withstood the treatment satisfactorily and that the renal lesion was tubular degeneration with intact glomeruli.

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OBSERVATIONS ON THE MIXTURE OF SEMENS: PRELIMINARY REPORT

DAVID S. CRISTOL

Physicians, when recommending artificial insemination, frequently encounter a marked degree of reluctance from the husband. Even when husband and wife prefer artificial insemination rather than adoption, the male partner frequently reveals considerable chagrin at being deprived of the opportunity of contributing his genetic background to the contemplated child. The psychologic trauma sustained by the non-contributing male partner reveals itself in a great variety of ways. In the great number of oligospermics it seems indeed unfortunate that their opportunity of contributing a part to the zygote should be no greater than the azoospermic or the necrospermic. It is for this group of patients that this study is being made.

On many occasions I have mixed the semens of numerous oligospermics, with varying degrees of oligospermia, and have observed no change in the type, character, or diminution in the duration of motility regardless of the patients' physical or blood types. Specimens from oligospermics have been mixed in pairs, in triads, and in tetrads with the identical result. Specimens from oligospermics of varying degrees and types have been mixed with normal semen specimens and the resulting mixtures have not demonstrated any lethal effects, or any diminution in number, or any alteration in the character or reduction in the duration of motility. Often I have observed that the resulting mixtures did appear to demonstrate an improvement in the duration of the motility which would exceed that of each component of the mixture.

These observations may prove to be a useful tool for the physician practicing artificial insemination. The reluctant male partner, who suffers from an as yet incurable oligospermia, might more enthusiastically enter into the agreement for artificial insemination if he realizes that with the mixing of his semen with that of the normal donor, there will be at least a mathematical possibility that he may contribute to the genetic background of his child.

A more detailed analysis of this study will be made at a later date.

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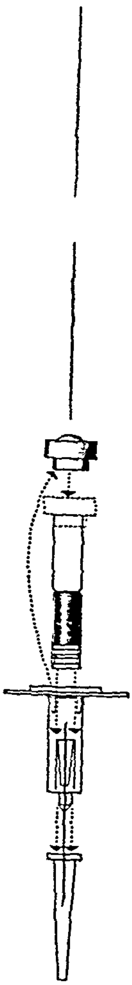

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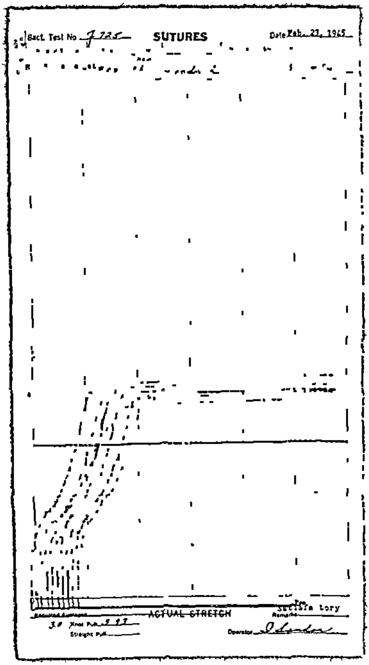

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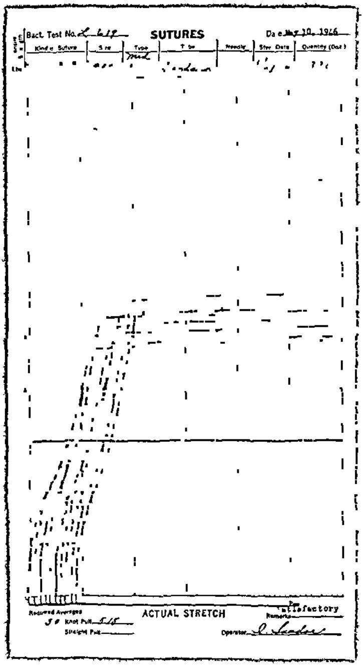

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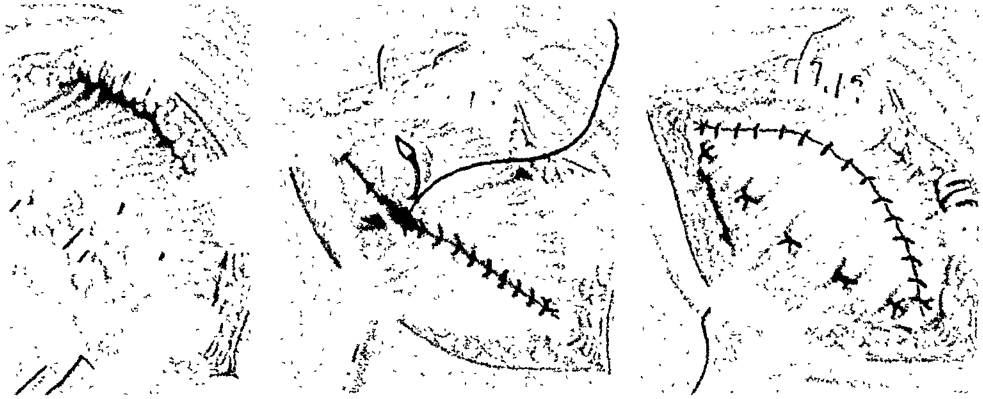

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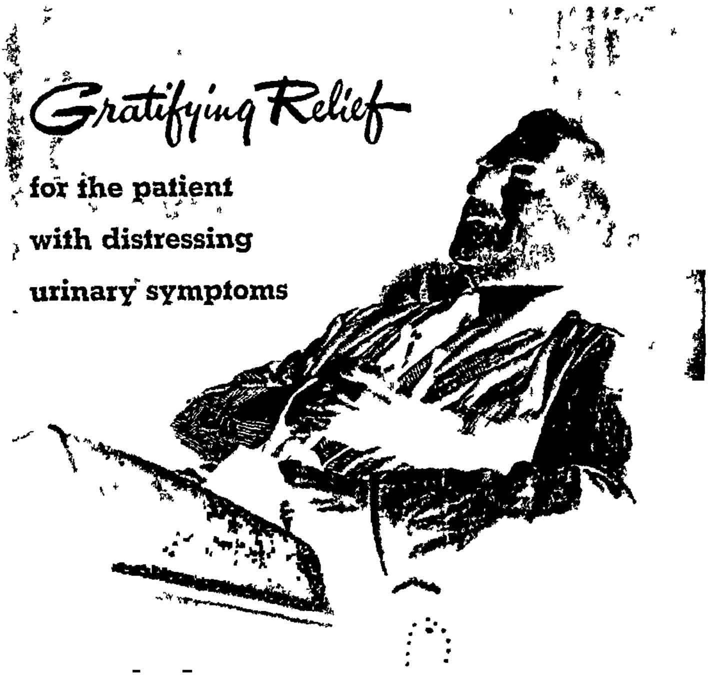

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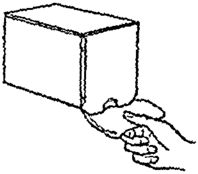

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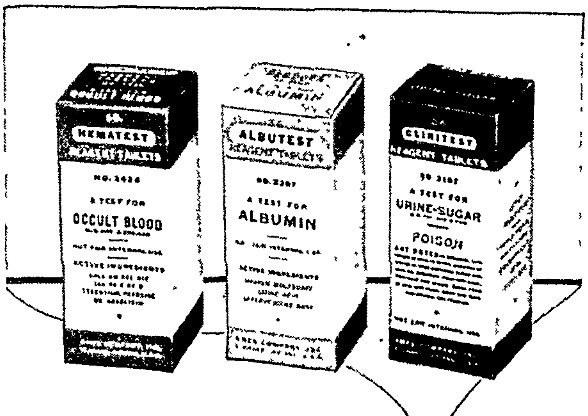

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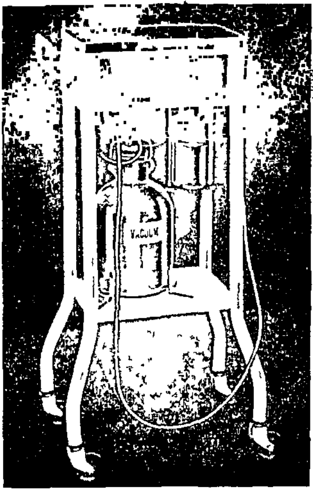

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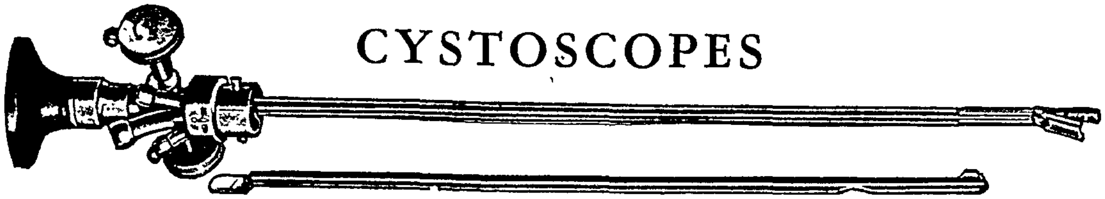

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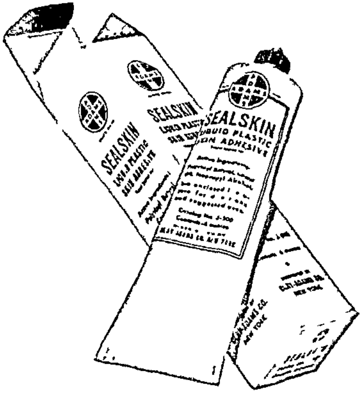

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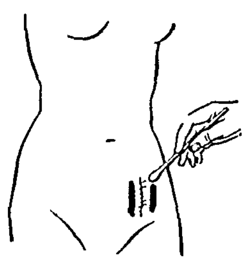

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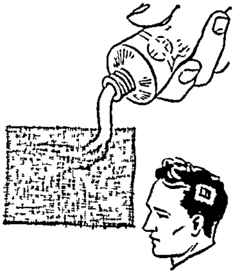

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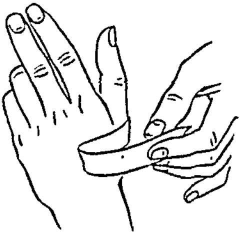

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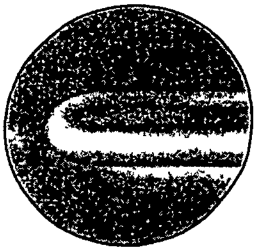

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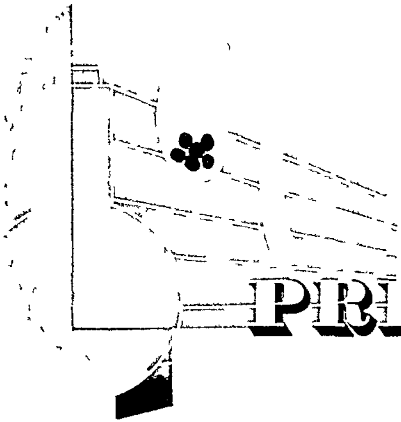

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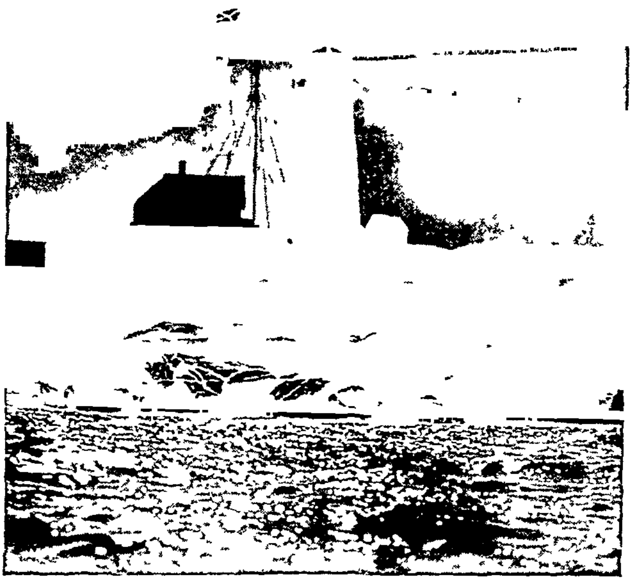

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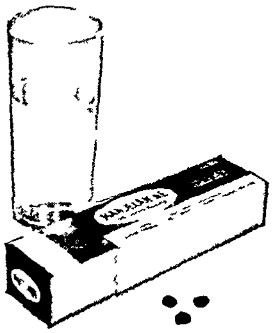

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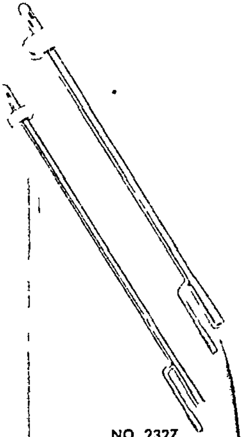

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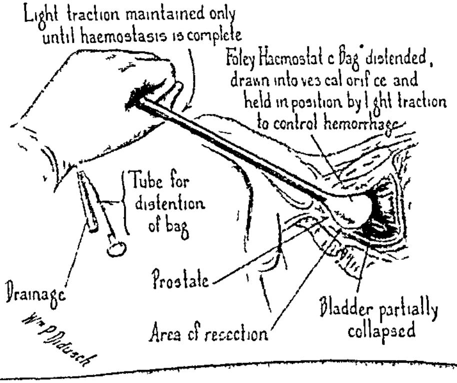
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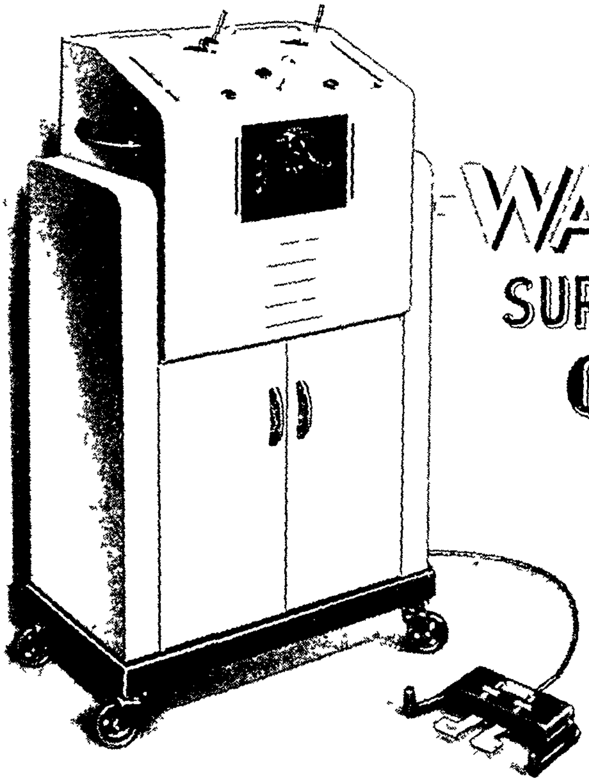

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THE SUPRARENAL CORTICAL SYNDROME: REPORT OF A CASE WITH CARCINOMA OF THE ADRENAL CORTEX

WILLIAM L. McLAUGHLIN AND JOHN P. BOWLER
The Urology Service
JARRETT H. FOLLEY
The Medical Service of the Hitchcock Clinic and Mary Hitchcock Memorial Hospital, Hanover, New Hampshire

The suprarenal cortical syndrome may be defined as the sum of metabolic changes produced in the body by the presence of an excessive amount of adrenal cortical steroids. Such over-elaboration of steroids may be the result of hyperplasia of the adrenal cortex brought about by the adrenotropic hormone of the pituitary gland. On the other hand, primary adenoma or carcinoma of the adrenal cortex may be the source of excess steroids. This latter condition is rare, yet it presents to the internist and urologist one of the most fascinating and challenging problems in all of medicine.

An understanding of the clinical manifestations of hormonal neoplasms of the adrenal cortex and a scientific approach to their surgical management are best gained by a study of adrenal cortical physiology.

Steroids are organic compounds having a molecular structure similar to cholesterol. By virtue of varying side atoms and chains of atoms they possess distinct biologic properties which put them in the category of hormones. The testes and ovaries as well as the adrenal cortex are known to be sources of hormonal steroids.

It has been well established that adrenal cortical steroids exert a profound influence on fluid and electrolyte balance; on protein, sugar and fat metabolism; on pigmentation; and on the masculinization and femininization of the body.

Some of the steroids of the crystalline fraction of whole adrenal extract include desoxycorticosterone, 17-hydroxy-11 dehydrocorticosterone (compound E of Kendall), dehydroisoandrosterone, estrone and progesterone. Bearing in mind that each of these is representative of a larger group of steroids, we believe that it may be worthwhile to consider briefly the biologic properties of each.

Desoxycorticosterone, frequently referred to as "doca", is the only adrenal steroid that has been synthesized. At present it is finding widespread clinical use in the treatment of Addison's disease. Its chief property is that of causing retention of water and sodium chloride and the elimination of potassium through an effect on the renal tubule. Exhibition of this substance in the normal human subject will produce abnormal sodium chloride and water retention.[8] Its use in patients with Addison's disease occasionally leads to hypertension and even cardiac failure.[23]

17-hydroxy-11 dehydrocorticosterone appears to have little to do with electrolyte and fluid balance. It is thought by most investigators to play a role in the conversion of protein to sugar, a process known as "gluconeogenesis." Al-

An adrenal tumor may be disclosed by roentgenography. By combining an excretory urogram with a plain film of the abdomen centered over the adrenals, one may occasionally demonstrate a mass displacing a kidney downward. The introduction of air into Gerota's capsule will frequently outline an adrenal neoplasm. Devised by Carelli in 1921, the technique of perinephric air injection has been perfected by Cahill in his study of the adrenal.[4,5,6,7] He has performed it in over 500 cases without fatality or complication.

In many patients exhibiting the Cushing's syndrome the differentiation between hyperplasia and tumor of the adrenal may be difficult. Since hyperplasia of the adrenals is frequently associated with a basophilic adenoma of the pituitary, all such cases should have a thorough evaluation of the intracranial status. From a diagnostic point of view it is unfortunate that basophilic adenomata are so small that neurologic signs and changes in the sella turcica are rarely produced. Often the diagnosis of hyperplasia or tumor of the adrenal is not established until the adrenals are exposed surgically. Walters[30,31,32] prefers surgical exploration of the adrenal areas in all suspects without preliminary airography, stating that in his opinion surgery is no more hazardous than airography.

SURGICAL MANAGEMENT

The optimum surgical approach to the adrenal is debatable. Walters believes the posterolateral extraperitoneal lumbar incision to be the one of choice. He has performed bilateral exposures to determine first the diseased side and second whether or not there is an adrenal on the other side. Cahill believes that the size of the tumor should govern the approach, reserving the transperitoneal incision for large neoplasms. Young devised a retractor which allows exposure of each adrenal simultaneously.

Clinical experience has brought out the fact that when features of the Cushing's syndrome are associated with an adrenal tumor, the removal of the latter invariably brings on a transient period of adrenal insufficiency. This is attributed to the fact that contralateral adrenal atrophy occurs in the presence of an excessive elaboration of metabolic steroids from a neoplasm.[5] On the other hand, patients exhibiting the adrenogenital syndrome without evidence of the Cushing's syndrome undergo surgical removal of an adrenal neoplasm without difficulty.[5] Contralateral adrenal atrophy, therefore, does not appear to occur in the presence of excess sex hormone.

The postoperative insufficiency state may be manifest as a frank Addisonian

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crisis, culminating in death within 48 hours. The high mortality in this group of patients is attributable to such a phenomenon. Crises are characterized by nausea and vomiting, weakness and prostration, marked elevation in temperature and pulse, with fall in blood pressure. There is reduction in the blood sugar and serum sodium and elevation of the serum potassium and nonprotein nitrogen.

One should be prepared to detect and combat adrenal insufficiency after removal of an adrenal tumor producing the Cushing's syndrome. Crises develop with great rapidity, which means that close observation of the vital signs must be made. When the insufficiency state seems imminent or has already become established, it should be combated by the administration of whole adrenal extract which contains the steroids controlling carbohydrate metabolism and by the administration of the synthetic steroid, desoxycorticosterone acetate, which helps repair fluid and electrolyte imbalance.[29] At the same time liberal amounts of sugar and sodium chloride should be given. Such replacement therapy must be continued until the remaining adrenal has recovered sufficient function to maintain life. This is usually a matter of a few days to a week. Large amounts of cortical extract may be given without danger. Desoxycorticosterone, however, has a much narrower margin of therapeutic safety, because of the rapidity with which it can produce fluid retention and cardiac embarrassment.

Since patients with either the Cushing's syndrome or Addison's disease show an increased susceptibility to infection, it may be wise to give penicillin prophylactically during and after the operative procedure. The high incidence of pulmonary atelectasis and pneumonitis following surgery of the renal areas calls for diligent nursing care to prevent the accumulation of secretions in the bronchial tree.

Estimation of the postoperative fluid and electrolyte requirements may be put on a reasonably accurate basis by frequent determinations of the hemoglobin, hematocrit, plasma chlorides, carbon dioxide combining power and blood sugar. Frequent transfusions of whole blood, plasma, and amino acids may be necessary.

Albright has pointed out that exhibition of testosterone in patients with the Cushing's syndrome will bring about a positive nitrogen, phosphorus, and potassium balance. The patient's skin becomes less thin, the muscles stronger, and the bones denser. This, of course, is not meant to be a substitute for surgery when neoplasm is present. It may, however, be important in the rehabilitation of a patient after removal of an adrenal cortical tumor.

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At the present time the status of partial resection of the hyperplastic adrenal is not well established. If too much cortical tissue be removed, control of the postoperative deficiency state is exceedingly difficult. It is to be hoped that a potent steroid controlling sugar metabolism will be synthesized for the handling of this situation. Walters suggests that hyperplastic adrenals should be partially resected and that later deep x-ray therapy to the pituitary should be given.

CASE REPORT

The following is the case history of a patient with carcinoma of the adrenal, whose clinical picture was that of an atypical Cushing's syndrome:

A 44 year old white male was admitted to Mary Hitchcock Memorial Hospital in March 1945, complaining of low back pain. His family history was non-contributory except that his mother died of carcinoma of the breast. Fourteen months previously he had undergone hemorrhoidectomy for hemorrhoids of several years' duration. At that time his blood pressure was recorded at 120 systolic and 80 diastolic. A few weeks postoperatively phlebothrombosis of both legs developed. After multiple severe pulmonary infarcts, ligation of the inferior vena cava just proximal to the bifurcation of the iliacs was carried out by means of a right lower quadrant, extraperitoneal approach. In a few months he was able to return to work. His ankles, however, swelled moderately after he had been on his feet for several hours. His past history was otherwise entirely negative. He had always been exceptionally vigorous and active.

Nine months before this admission members of his family noticed progresive "bloating" of his face, particularly about the cheeks and under the chin. For the past 1½ months he complained of low back pain which was aggravated by motion. There was no history of injury or heavy lifting.

On examination he was found to have normal respirations, pulse, and temperature. The blood pressure was 140 systolic and 90 diastolic. His face appeared slightly "moon-shaped." The skin was thin, dry and atrophic. No rubor, striae, or acne was present. The musculature of the arms and legs was atrophic. No abdominal adiposity and no "buffalo-hump" in the cervico-thoracic region could be made out. The area of liver dullness appeared to be abnormally small. Bilateral spermatoceles were present.

The hemoglobin was 15.3 gm. per 100 cc blood and the red cell count 5,000,000. The white cell count was 11,400 with 83 per cent polymorphonuclear leucocytes and 16 per cent lymphocytes. The sedimentation rate was 30 mm. in 1 hour. The urine was negative. The serum phosphorus, the serum calcium, the serum alkaline phosphatase, the serum albumin, the serum globulin, and the serum cholesterol were within normal limits. The serology was negative. A bone marrow smear contained no abnormal forms. The basal metabolic rate was consistently low, ranging between minus 29 per cent and minus 32 per cent.

The roentgenograms of the spine revealed marked osteoporosis with compression fractures of the second, third, and fourth lumbar bodies. The chest was negative. Excretory urograms showed normally functioning kidneys with the right kidney questionably depressed by a mass above it. Airograms of the adrenals were suggested, but not carried out at that time.

The patient was placed in bed with the spine in hyperextension, and accessory calcium and vitamin D were given. Because of his low basal metabolic rate, a regime of desiccated thyroid by mouth was instituted. He remained in the hospital 6 weeks and was discharged on the same regime and with a hyperextension brace.

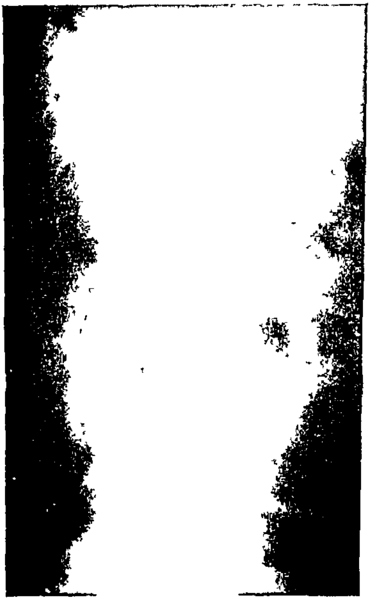

FIG 1. X-ray of spine, showing osteoporosis with collapse of lumbar bodies

In May 1945, one month later, he was readmitted because his general condition had grown worse. He had gradually fallen into a psychotic state characterized by severe mental depression and feelings of unworthiness. His blood pressure was higher, ranging between 150 and 180 systolic, 90 and 110 diastolic. His pulse rate ranged between 90 and 120. These changes persisted following discontinuation of the thyroid medication. The basal metabolism rate was still minus 14 per cent.

Physical examination revealed further wasting of the arms and legs, but was essentially as before

The glucose tolerance curve, the hematocrit, the plasma chlorides, the carbon dioxide combining power and the plasma proteins were within normal limits.

The roentgenograms of the spine disclosed further osteoporosis with more narrowing of the vertebral bodies (fig. 1). The long bones and the skull appeared normal. Perinephric air insufflation (fig. 2) revealed a rounded mass above the right kidney. The outline of the left adrenal appeared large.

Fig. 2. Perinephric air insufflation, showing tumor above right kidney

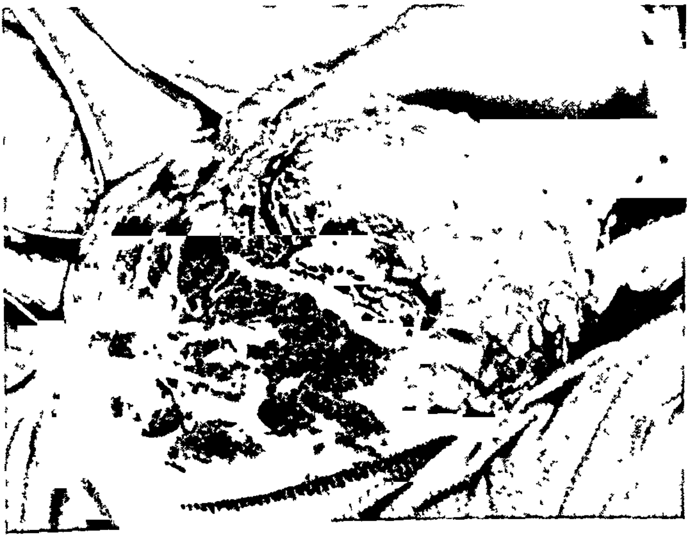

Fig. 3. Gross appearance of adrenal cortical carcinoma at time of operation

On the sixteenth hospital day he received a transfusion of 500 cc whole citrated blood. On the eighteenth day he was given nitrous oxide-oxygen and ether anesthesia and the right adrenal area was explored through a posterolateral incision. The twelfth rib was resected. A neoplasm above the right kidney was found (fig. 3). The biopsy and immediate frozen section revealed normal-appearing adrenal cortical tissue. It was then noted that the biopsy had been taken from the normal adrenal gland which was present as a thin shell on the anterior surface of the tumor. A small incision was made anteriorly into the peritoneal cavity. Palpation of the left adrenal area was not entirely satisfactory, but no abnormality was found. The liver had been displaced upward and rotated by the tumor, but felt normal. The tumor was well-encapsulated and was easily dissected. Many dilated veins, however, were encountered. Only a small pedicle was isolated and easily ligated. During the extraction of the tumor a small amount of necrotic tissue spilled into the wound. These fragments were removed, but, as a precautionary measure, the wound was thoroughly swabbed with liquid ether. Two Penrose drains were brought out through the posterior angle of the wound. The operation lasted 2 hours and was well tolerated by the patient. During the procedure he was given 1000 cc whole citrated blood.

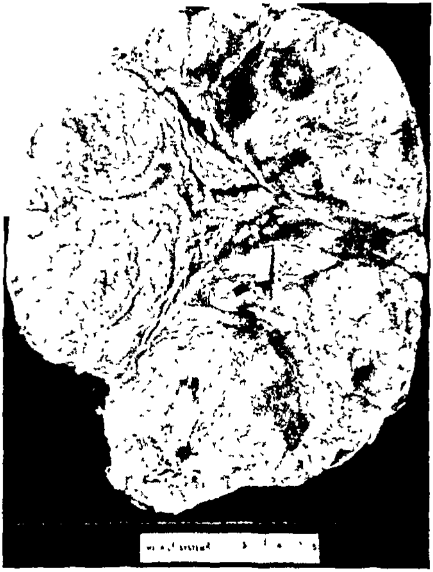

FIG. 4. Sectioned surface of adrenal cortical carcinoma

The neoplasm weighed 1000 gm. Except for an area of necrosis the capsule appeared intact. The sectioned surface (*fig. 4*) revealed different sized nodules of grey-yellow tissue interspersed with areas of hemorrhage and necrosis. Microscopically there were two distinct patterns. In one (fig. 5, *A*) the cells were characterized by clear, light-staining cytoplasm and prominent nuclei with many mitotic figures. In the other (fig. 5, *B*) the cells were smaller, darker and

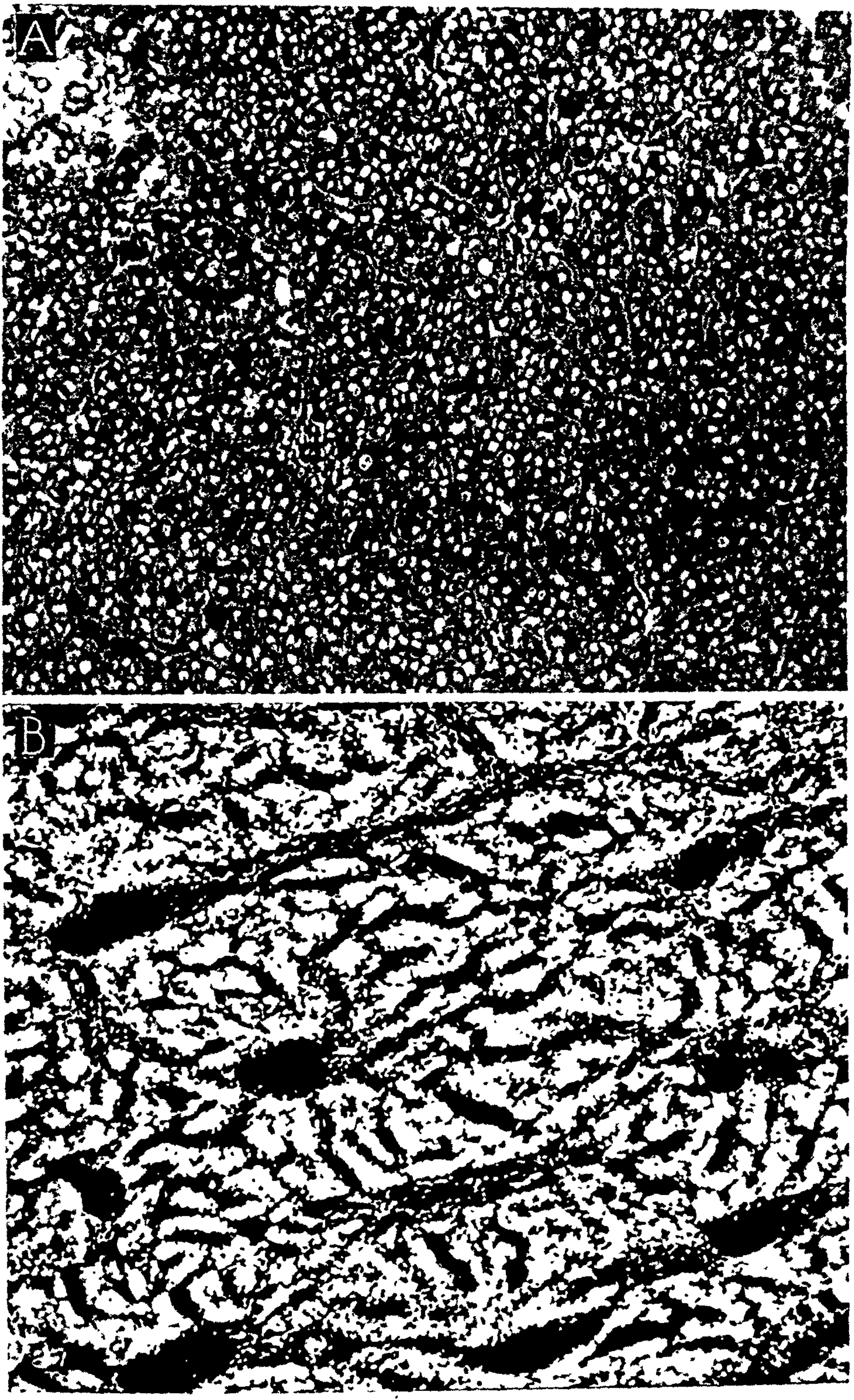

FIG. 5. Photomicrographs of adrenal cortical carcinoma. *A*, showing clear, vacuolated cytoplasm and mitotic figures. *B*, showing small, dark staining cells grouped about dilated blood vessels.

grouped in cords about widened vascular channels. It was the consensus of several pathologists that this was a cancer of the adrenal gland.

In the immediate postoperative period dramatic changes occurred (fig. 6). The blood pressure dropped, averaging about 100 systolic and 70 diastolic. The temperature, pulse, and respirations rose. Despite the unfavorable trend in his vital signs, his mind became much clearer and he was no longer depressed.

In an effort to combat what appeared to be an adrenal insufficiency state he was given adrenal cortical extract (Eschatin) by vein, and desoxycorticosterone acetate (Cortate) intramuscularly (fig. 6). For 4 days he received a slow, continuous infusion of 5 per cent dextrose in saline containing penicillin, which brought his total fluid intake to approximately 2500 cc per 24 hours. Despite a regime of turning, deep breathing and coughing, on the first postoperative day he was found by x-ray to have a small amount of atelectasis above the right diaphragm. He became slightly dyspneic and was placed in an oxygen tent for 24 hours.

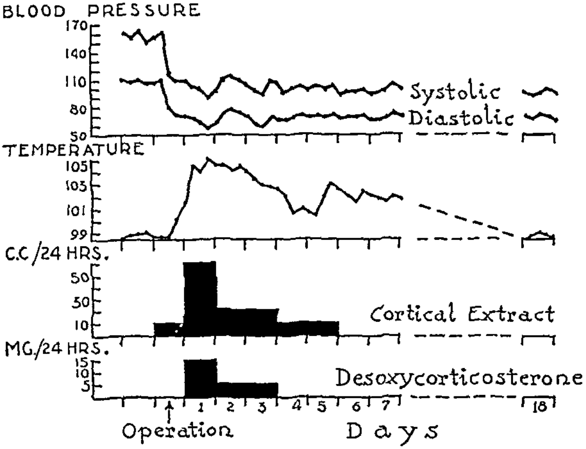

FIG. 6. Showing changes in vital signs and replacement therapy in postoperative course

On the first postoperative day a blood sugar of 18 mg. per 100 cc was obtained. The non-protein nitrogen, plasma chlorides, carbon dioxide combining power, plasma proteins and hematocrit were normal at that time.

On the sixth postoperative day he appeared to be in a salt and fluid retention phase with lowered urinary output, generalized edema, lowered hematocrit and lowered plasma proteins There was no clinical evidence of cardiac failure. This persisted despite the fact that he was given several transfusions of plasma and whole blood and despite the fact that desoxycorticosterone and supplementary salt had been discontinued on the third postoperative day. On the seventh postoperative day he was allowed up out of bed with a brace on his back.

During the second and third postoperative weeks the generalized edema gradually disappeared except in the lower legs. His mental state, which immediately after the operation showed improvement, was again characterized by depression and marked aversion to food. He had to be tube fed for 3 days and was given daily infusions of amino acids.

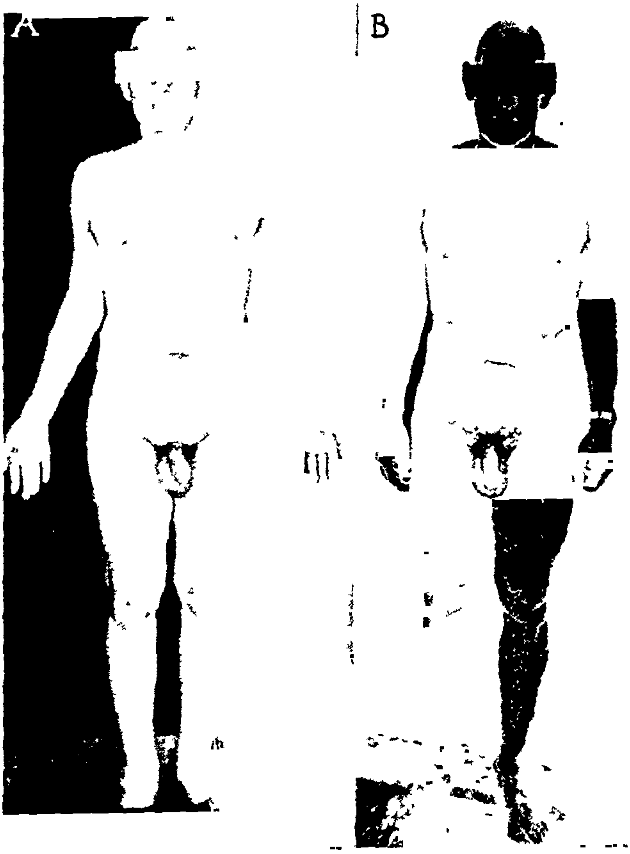

FIG. 7. *A*, Full view of body 6 weeks, and *B*, 13 months following removal of adrenal carcinoma.

The wound healed well. Despite the fact that no focus of infection could be found, the patient's temperature remained elevated from 2 to 4 degrees until the eighteenth postoperative day.

On the thirty-sixth day he was started on a course of testosterone propionate. Striking improvement appeared to coincide with the institution of this therapy. At the time of his discharge on the forty-seventh postoperative day he was stronger and was no longer depressed (fig. 7, *A*).

As an out-patient he was given periodic injections of testosterone propionate intramuscularly, and in the course of the next 11 months he received 75 mg. weekly for a total dose of 2000 mg.

His general condition slowly improved, although the edema of the lower legs persisted. The hemoglobin and plasma proteins remained low. He was placed on a high vitamin, high protein and high calcium diet.

Two months after the operation the spine appeared to have undergone slight recalcification. He was then allowed to be up and about as desired with a hyperextension brace on his back. By the end of the fourth month the edema of the lower legs had disappeared.

In June 1946, thirteen months after removal of the tumor, he appeared to be in excellent health (fig. 7, *B*). The pulse rate was 80. The blood pressure was 104 systolic, 70 diastolic. The swelling of the face had completely disappeared. The musculature of the arms and legs had improved. The wound was solid and no abdominal masses could be felt.

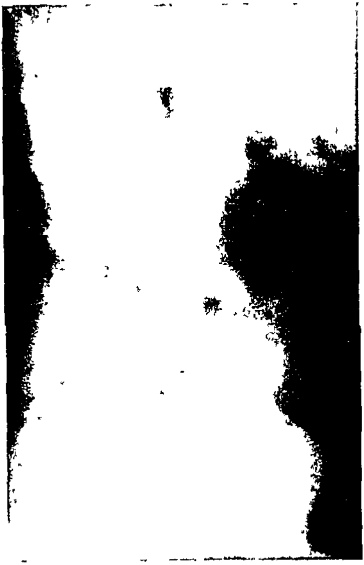

Fig. 8. X-ray of spine 13 months after removal of tumor, showing recalcification

There was no anemia. The white cell count was 7,000 with 55 per cent lymphocytes. The blood sugar, non-protein nitrogen, plasma chlorides, carbon dioxide combining power were within normal limits. The serum proteins, however, were still low.

The spine appeared to be completely recalcified (fig. 8), although narrowing of the bodies remained. An x-ray of the chest was negative.

For the past 2 months he has been at a full time job and has returned to his normal recreations including golf.

COMMENTS

The replacement therapy during the patient's postoperative adrenal insufficiency phase was probably not adequate in regard to whole adrenal extract, the one containing the carbohydrate-controlling factors. A larger amount, had it been given, might have carried him through the insufficiency phase with less shock.

It is difficult to explain the postoperative fluid retention phase which persisted despite several transfusions of whole blood and plasma. The exhibition of desoxycorticosterone may have precipitated it, but it should be noted that only a small amount of this steroid was given and not at any time did hypertension develop, one of the characteristic features of desoxycorticosterone poisoning.

Testosterone propionate may have aided in the rehabilitation of this patient. It is possible that this steroid, in addition to building up the muscles and other tissues, increased the rate of recalcification of the spine by speeding up the formation of protein matrix on which calcium and phosphorus could be deposited.

The slight, relative increase in the number of neutrophils at the height of the patient's altered metabolism due to the adrenal tumor and the shift to relative lymphocytosis and neutropenia after removal of the tumor are probably manifestations of the effect of one of the adrenal cortical steroids. The lymphocytosis at present suggests an adrenal insufficiency state, although there are no other stigmata of such a condition.

To summarize, we have presented a brief discussion of the suprarenal cortical syndrome and the case history of a patient exhibiting many of the features of this syndrome. Attention has been called to the fact that a so-called "classical" picture will seldom occur because of the variances in the predominant steroid or steroids. Following the removal of a large carcinoma of the right adrenal, this patient went into a state of adrenal insufficiency, which, because of its Cushing's syndrome-like background, could be anticipated. His recovery was slow, but apparently complete. While it is to be regretted that it was not possible to document this case with an analysis of the type or types of excess steroid, the entire picture indicates that we were dealing with an adrenal cortical neoplasm which produced steroids of considerable biologic activity.

CONGENITAL ARTERIOVENOUS ANEURYSM OF THE RENAL ARTERY[1]

ROBIN PEARSE AND R L MACMILLAN

From the Departments of Urology and Pathology, Toronto General Hospital, Toronto, Canada

A well preserved man 60 years of age, without previous warning or other symptoms, found his urine bright red with blood Twenty four hours later the blood was sufficient to clot in the bladder and produce some difficulty in micturition The bladder was irrigated by the patient's physician, through a catheter with some relief, but as the hematuria persisted, arrangements were made to send the patient to Toronto, where he arrived on October 11, 1945, six days after the onset of the bleeding

The hematuria abated considerably during the journey The patient denied any trauma or violent exercise Past history was irrelevant except that a small stone had been passed from the right kidney 10 years previously

The blood pressure was 160/60, nonprotein nitrogen 35, urine bloody, specific gravity 1022, no sugar Abdominal palpation revealed no abnormality, and rectal examination showed only slight adenomatous enlargement of the prostate

Cystoscopy showed a few small recent clots in the bladder, which were washed out, and an old clot adherent to the lip of the left ureteral opening The prostate was only slightly enlarged, and no stone, tumor or diverticulum could be found Catheters passed easily to both renal pelves and clear urine, which presently became slightly tinged with blood, probably traumatic in origin, came from the right side Nothing came spontaneously through the left catheter, but on irrigation a few drops of very thick, bloody fluid were obtained

Plain x ray films were negative for stone and films exposed after injection of 12 5 per cent sodium iodide were reported upon by the radiologist (Dr A C. Singleton) as follows "The pyelogram shows normal right kidney pelvis with normal major and minor calyces On the left side there appears a globular pressure defect on the middle and upper calyces, and again between the middle and lower calyces The findings are in keeping with either a cystic kidney or possibly an early hypernephroma There can be seen a soft tissue mass anterior to the left kidney pelvis, which appears to be producing pressure upon the kidney pelvis " See figure 1

The hematuria stopped after the pyelogram had been made, and the patient was prepared for transperitoneal nephrectomy, which took place 4 days after his admission to the hospital

Spinal anesthesia (nupercain supplemented by inhalation of cyclopropane and oxygen) was used The blood pressure was 160/60, pulse 100 An incision was made through the middle third of the left rectus muscle from just above the costal margin to a little below the umbilicus The peritoneal cavity was opened and the descending colon and small intestine drawn to the midline.

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[1] Read at annual meeting, Western New York and Ontario Urological Society of the Central Section, American Urological Association, Alexandria Bay, N Y , September 14, 1946

The posterior layer of peritoneum was divided along the white line, the anterior layer of the perirenal fascia incised and the large and small bowel retracted across the midline, exposing the kidney with its blood supply.

A large vessel was seen crossing the renal pelvis to enter the hilus. On palpating this vessel a vibratory thrill was felt. A little more dissection disclosed an aneurysm of the renal artery.

There being no longer any contraindication to manipulating the kidney, which appeared to be normal, the ureter was clamped, divided and ligated. The kidney was then lifted from its bed and turned forwards. One clamp was placed on the renal artery proximal to the aneurysm and two on the renal vein. The vascular pedicle was divided and the kidney removed. The renal artery and vein were tied separately and then a third ligature placed around the two vessels. The posterior peritoneum was repaired with catgut, the anterior abdominal wall with buried figure of 8 sutures of stainless steel wire, and the skin with waxed thread. The blood pressure was then 125/75, pulse 95. Five hundred cubic centimeters of blood were given during the operation and 2000 cc glucose in saline afterwards. The patient made an uneventful recovery.

Fig. 1. Retrograde urogram

Pathologist's report: At the mesial border of the left kidney, towards the lower edge of the hilus, was a saccular aneurysm 3 cm. in diameter, formed by a dilatation of the lower branch of the renal artery.

A small saccule extended from the anterior part of the aneurysm. This saccule communicated freely with the main aneurysm through an opening 1 cm. in diameter.

Neither aneurysm nor saccule contained blood clot. The wall of the main aneurysm measured 2 mm. in thickness, it was smooth, whitish, tough and flexible, and its inner surface showed small yellowish patches and flecks of atheroma. The wall of the saccule was rigid and contained calcium.

Inside the aneurysm was a further opening 0.5 cm. in diameter communicating with a large irregular cavity. The lining of this cavity had a glistening surface and was very adherent to the underlying renal substance. It was thrown into folds by the pressure of adjacent calyces and contained no atheromatous deposits. The cavity was drained by a main branch of the renal vein.

The above findings demonstrated a venous aneurysm and an arterial aneurysm with an arteriovenous communication.

The pressure of the venous aneurysm has caused considerable distortion and narrowing of the cortex and pyramids of the lower pole of the kidney. No communication could be found between the renal pelvis and either of the aneurysm. See figure 2.

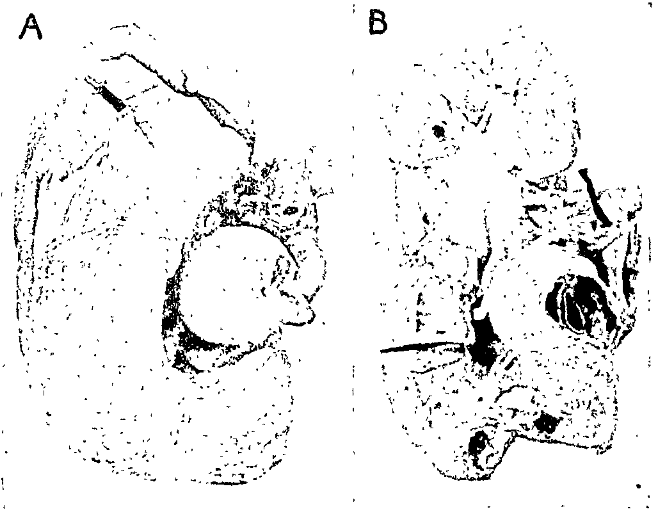

FIG. 2. *A*, Posterior aspect of kidney, showing arterial aneurysm. *B*, Further dissection, showing arterial and venous aneurysm.

Histologically, the wall of the arterial aneurysm consisted of a dense inner layer of collagen and elastic fibres, with an outer layer of loose connective tissue containing small blood vessels. The venous aneurysm differs in that the dense layer of collagen was narrower and a well defined internal elastic lamina was present.

The kidney itself showed a marked increase in peripelvic fat, especially towards the lower pole. The pelvis was slightly dilated. On the surface of the kidney were a few retention cysts varying in diameter up to 0.5 cm. The cortex and medulla together measured no more than 2 cm. at any point, and in some areas only 1.3 cm.

The capsule was adherent over the lower pole, and in this area there was marked destruction of the medulla.

COMMENT

Kahle and Schenken recently reported an aneurysm of the renal artery which developed after partial nephrectomy. These authors reviewed the literature and enumerated previous cases, but failed to include one by Levine reported the preceding year. The present case would, therefore, seem to be the eighty-first in the literature and the first case of congenital renal arterio-venous aneurysm on record.

The etiology is obscure; probably a gradual dilatation occurred of one or more of the small cross communication channels, which always are present between large arteries and veins lying in close apposition. Such dilatation would take many years to attain the size of the specimen under discussion.

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ANURIA FOLLOWING BLOOD TRANSFUSION
REPORT OF TWO CASES[1]

N. E. BERRY

It was an unusual coincidence that within a few weeks, time we had, in the same town, 2 cases of anuria following blood transfusion. In neither case was there gross incompatibility of the blood grouping, but some equally serious reaction had occurred. Since those factors which cause such reactions are now being more generally studied and recognized it seemed worth while presenting these cases.

CASE REPORTS

Case 1. Mrs. H., aged 37, had a Caesarian section December 11, 1945 for her fourth pregnancy, the last 2 of which had been sections. She had had 1 previous transfusion and the afternoon of operation was given 450 cc. whole fresh blood. The evening of operation she had a rise of temperature to 101° which fell promptly to normal and remained there. Her condition was satisfactory on the first and second postoperative days and she passed 11 and 16 ounces of urine, but on the third day it fell to 2½ ounces. For the next 3 days the output was between 3 and 4 ounces. The urine was at first clear, but became turbid and showed much pus and staphylococci.

I saw her 6 days after operation. She was very anemic and weak, but had no special complaints. She did not show any evidence of jaundice and was only moderately dehydrated. A spinal anesthetic was given and a cystoscopic examination with catheterization of both ureters was done. There was no obstructive uropathy and no urine in the bladder or kidneys. She was turned on her side and the right kidney exposed. It was not delivered, but a small incision was made in the true capsule, the finger passed in and decapsulation completed. The kidney was slightly enlarged and pale. She was given a further transfusion of Rh negative blood and her temperature rose to 103°. It was normal the following morning, but her abdominal wound opened and had to be resutured. She passed 7 ounces of urine that day, 7 the next day, 15 the following day and then promptly got well.

Microscopic examination of biopsy from her kidney showed some of the glomeruli to be atrophic. A few had shedding of capsular epithelium. The convoluted tubules showed cloudy swelling and necrosis of their superficial cytoplasm. The lumina of some were completely obliterated by hyaline, granular, epithelial and blood cells. The stroma was edematous (fig. 1, A).

Case 2. Mrs. A., aged 48, was operated upon January 14, 1946 when a hysterectomy was done for fibroids. She was given a transfusion of 450 cc. whole blood the same day. She had no reaction and no fever. There was some oozing from the wound that night and her temperature the next day was 100°. The following morning she was catheterized because she had not voided and 2 ounces bloody urine obtained. Her stools were also tarry, there was some oozing from the nose and she had vomiting of a coffee ground character. Twelve hours later she was again catheterized and 2 ounces bloody urine obtained. She continued to pass 2 to 3 ounces of urine daily, and it became free of blood but contained pus. She also vomited a little each day; 4 days postoperatively her skin and conjunctivae became icteric and by the fifth day she had a nonprotein nitrogen of 115 mg.

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[1] Read at meeting Western New York and Ontario Urological Society, American Urological Association, Thousand Islands Club, September 13, 1946.

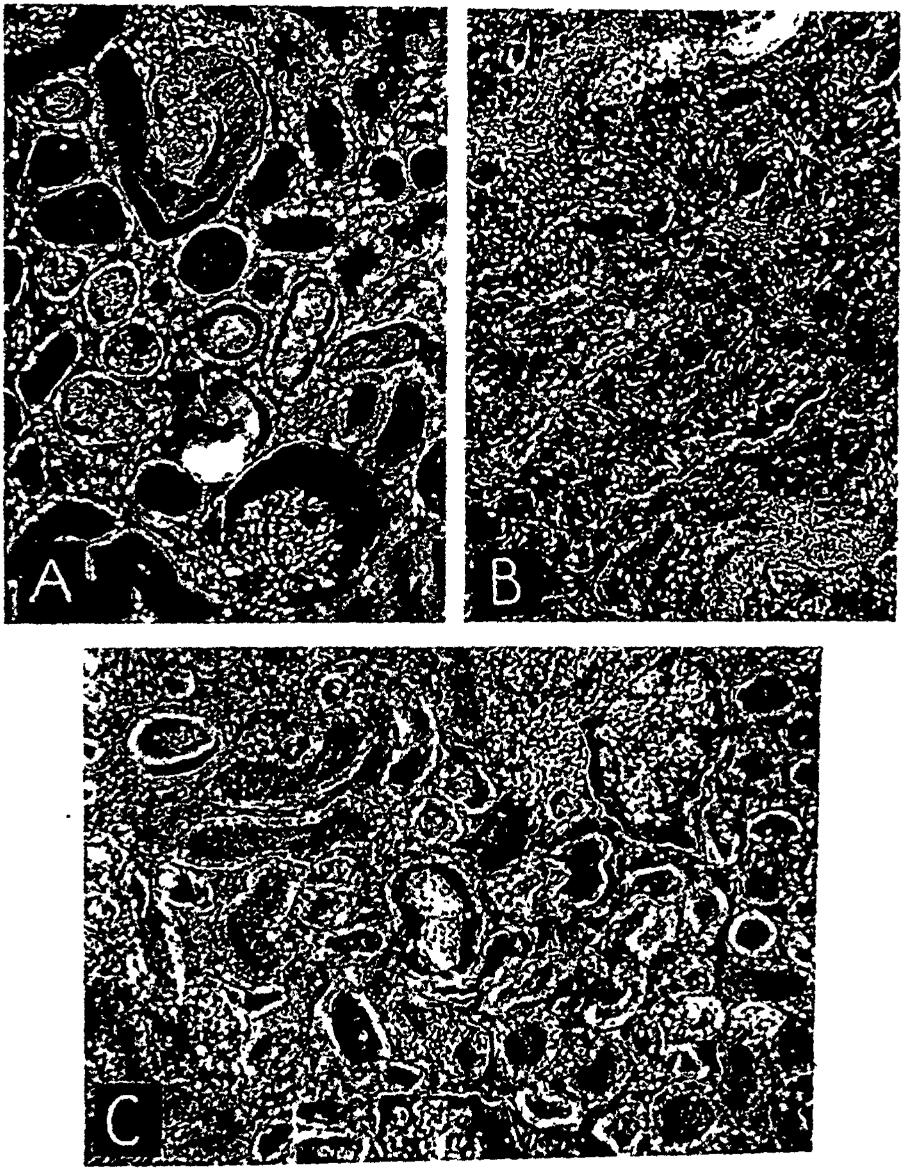

Fig. 1. *A*, Showing distended glomerulus and tubules. Note casts and degeneration of tubular epithelium. *B*, From medulla, showing cast, cloudy swelling and fatty degeneration of epithelium, and round cell infiltration. *C*, From fatal case showing changes similar to *A*.

I saw her 8 days after her operation. She was very confused, dehydrated and obviously uremic. A spinal anesthetic was given and a cystoscopic examination done with catheterization of ureters. There was no obstruction and no urine in the bladder or kidneys. She was turned on her side and a right decapsulation done. The kidney was slightly enlarged, pale and edematous, as in the other case. She passed 2 ounces of urine that day and 4½ the next but her condition continued to deteriorate and she died 48 hours after operation and 10 days after her transfusion.

The kidney was obtained at autopsy and was slightly enlarged. The cortex was swollen and pale, the pyramids of the medulla congested. Microscopically the main change was a blocking of the tubules with altered blood cells and pigment. The tubules which had been blocked were mainly Henle's loop and the collecting tubules in the medulla. The tubular epithelium showed cloudy swelling and some fatty degeneration. The glomeruli showed a relative absence of blood in the capillaries and distention of Bowman's capsule. The stroma was edematous and infiltrated with group of lymphocytes (fig. 1*B* and *C*).

Through the courtesy of Dr. Lubinski of the Jewish General Hospital, Montreal, we have been able to have complete studies of the blood of donor and recipient in the case which recovered. They were both group O, the donor being Rh positive and the recipient Rh negative. No anti-Rh agglutinins were present in the recipient's blood but blocking antibodies and conglutinins were present in a dilution of 1:1. This examination was not made till 6 months after the illness. Dr. Lubinski concludes that the patient must have had a reaction due to Rh incompatibility and that she had previously been sensitized by transfusion or pregnancy. In the patient who died no such studies were possible, but it could not have been a gross error of typing though of course if she were a group A or B there might have been a minor error with some of the sub-groups.

I know of a third case which was seen by an assistant. The patient, a young W.A.C., was operated upon for a ruptured ectopic pregnancy and was given a transfusion. Anuria developed and the patient died in about 10 days. Cystoscopic examination had been done and there was no mechanical obstruction. Presumably she was Rh negative and it is almost a certainty that she was highly sensitized and transfusion without such determination was asking for trouble.

DISCUSSION

Our chief interest in these cases concerns the value of decapsulation. Abeshouse has presented a masterly review of this problem. He was able to find only 3 cases of post-transfusion anuria which were treated by unilateral decapsulation, with excellent results in each case. Ravich attributed the beneficial affects of rapid decapsulation to the relief of pressure which broke a vicious chain (presumably sympathetic nerves) and reflexly started secretion in the opposite kidney. Daniels reported 7 deaths in a series of 13 non-operative cases.

It is generally agreed that decapsulation is not to be employed until medical and supportive measures have failed. Flo and Cummings, who reported 1 of the operative cases, maintained that an arbitrary period of 1 week is sufficient to try conservative measures. They stress that if you wait too long cortical necrosis may occur.

In considering conservative treatment Lattimer calls attention to the fact that these patients die from cerebral and pulmonary edema (followed by pneumonia) and that in uremic patients in general it is most important to limit fluid intake to 1000–2000 cc daily. He also stresses the importance of alkalinization with soda bicarbonate. It increases the solubility of sulfa drugs or *hematin*; it may counteract some of the uremic acidosis and it may keep the blood potassium from rising to toxic levels. The work of Baker and Dodds, and Degowin has demonstrated that in animal experiments acid hematin pigment will precipitate in the renal tubules when the urine is acid and that tubular damage resulting therefrom produces the clinical picture of uremia similar to that in man. When the urine is alkaline the hemoglobin is excreted without damage.

Lattimer states that decapsulation seems to be of value only when renal edema is sufficient to compress the nephrons. He reported 1 such case, a transfusion reaction in a postpartum female and recovery followed bilateral decapsulation. He believes it should be used only where there is evidence of such edema and suggests 14 days of conservative treatment. Though both of our patients were clinically dehydrated, the kidneys showed both gross and microscopic edema.

Colby quotes Talbott who reported a case of anuria following blood transfusion which had a unilateral decapsulation on the fourth postoperative day and which recovered. She had catheters placed in each ureter and the urine started about 24 hours later in equal amounts from both sides. They decided that the operation was of no benefit and Colby stated that no other case has had decapsulation at the Massachusetts General Hospital.

Abeshouse however concludes that progressive oliguria and anuria are indications for decapsulation and that early decapsulation has proven to be an effective method of combating the anuria associated with posttransfusion nephrosis.

It is notable that most of the reported cases have occurred in women and the special danger of reactions following transfusion in postpartum cases is a repeated observation. The reason is not given but it is clear that in the great majority of these cases it is due to Rh sensitivity, pregnancy being the commonest cause. It must be recognized that no female under 45 years of age should be given a transfusion without Rh determinations and if negative only Rh negative blood should be given. This holds true after 45 if they have had children or previous transfusions. Recognition of this will prevent reactions such as occurred in these cases (assuming that proper cross check is done) and will avoid sensitizing females which is especially important in their child bearing period.

SUMMARY

Two cases of anuria following blood transfusion are presented. Both had decapsulation of 1 kidney; 1 recovered and 1 died. Rh sensitivity was a proven factor in 1 case and a probable factor in the other.

Determinations of Rh factor should be done before transfusion in all women who have had children.

Thorough alkalinization of the blood and urine is of value in treating post-transfusion anuria and should be considered as possibly worthwhile in all transfusions.

Fluid intake should be limited instead of forced in anuria to avoid cerebral and pulmonary edema.

Decapsulation can be made a simple procedure and should be considered in every case of posttransfusion anuria. It should certainly be done where anuria has persisted for a week, in spite of good medical treatment, or where there is edema.

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TRANSPLANTATION OF THE URETERS AND TOTAL CYSTECTOMY[1]

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Transplantation of the ureters and total cystectomy is a surgical campaign of considerable magnitude which carries a postoperative mortality of at least 10 to 20 per cent. Radiation therapy for bladder cancer carries a much lower immediate mortality, so that before advising the surgical program the surgeon should have some definite reasons in mind.

First of all, how effective is radiation in the treatment of bladder cancer? Three hundred consecutive bladder cancer records at the Memorial and New York Hospitals from 1932 to 1938 inclusive have been reviewed in detail. Papilloma is excluded, and it must be stressed that our pathologists' diagnoses are rather severe, excluding from the cancer classification even atypical papillomas which are commonly called low grade malignant. Only 52, or 17 per cent, are known to have survived 5 years and only 27 of these could be called free of cancer 5 years after diagnosis, 9 per cent. These 27 cases, representing 5 year successful results, will not all stand a critical review as "cures", since in at least 5 there is some doubt in regard to the diagnosis of cancer, at least 5 have poor records of their condition at the 5 year anniversary, and at least 5 subsequently have died without a reliable record of cause of death being obtained. Furthermore, 3 were clinically free of disease because cystectomy had been done after the failure of radiation therapy. All points considered, it would be reasonable to say that by our radiation methods of the 1930's the 5 year successful result rate was approximately 6 per cent. The average survival was 24.5 months for a group of 316 with a complete follow-up of 3 years or more.

This compares poorly with similar figures obtained from life insurance companies for the general population at the same average age in which the average survival is 15 years with approximately 88 per cent surviving 5 years. This compares only barely favorably with results of non-treatment as reported elsewhere in which the average survival was 18.8 months with approximately 10 per cent surviving 5 years. Obviously, there is room for considerable improvement in both survival rate and cure rate. Besides, the morbidity was very high. No metastases were found in 49 per cent of 53 autopsies performed at these hospitals which are not for terminal care. Certainly this 49 per cent did not die of carcinomatosis and it is equally certain that they were not saved by radiation. Most of them died of upper tract obstruction and sepsis so the suggestion is readily apparent that if the upper tracts could be protected, a longer survival would be likely regardless of the treatment of the cancer itself.

A few outstandingly good results were obtained, indicating that it is possible for radiation to cure bladder cancer but one must conclude that on a large scale basis the results of radiation treatment are poor Perhaps the very nature of the disease will not allow improvement with the means now available but surely an attempt at improvement seems warranted, especially as the total failure of the new treatment would not result in a huge loss to the whole group so treated

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[1] Read at meeting of Western New York and Ontario Urological Society, Central Section of the American Urological Association, Thousand Islands, Alexandria Bay, N. Y., September 14, 1946.

The simplest surgical treatment of bladder tumors is local destruction by fulguration On reviewing our old and recent records we find very, very few good results thus obtained and the overwhelming majority proved to be no more than papilloma, and not cancer histologically, especially when the result was not obviously a failure Most of these few good results were obtained with small, well localized, and low grade lesions but there were so many apparently similar cases which resulted disastrously that the criteria for choosing candidates was not evident Few internal cancers are cured by simple local destruction and a complete follow-up on histologically proven bladder cancer indicates no major exception in our experience

Thirty-three bladder resections done within the past 5 years have resulted already in 11 known recurrences in the bladder and 3 postoperative deaths Twelve of the 33 are now known to be dead Even so, the average survival is 20 months in spite of the fact that the follow-up is necessarily less than 1 year in 14, and less than 2 years in 17 Several patients have had excellent results thus far, but the impression is unavoidable that in our anxiety to preserve bladder function and avoid more immediately hazardous surgical procedures we attempted resection on lesions too large, on lesions where the margin of removal was necessarily small, and on lesions with a tendency to multiple origination within the bladder

Total excision of the bladder is usually not a difficult or dangerous operation in itself as partially witnessed by only 2 deaths in over 77 cases, a mortality of $2\frac{1}{2}$ per cent or less However, *the real surgical problem is the satisfactory permanent diversion of the urinary stream prerequisite to cystectomy* Transplantation of the ureters to the skin is a relatively simple procedure and in our experience almost all postoperative deaths can be obviously attributed to the patients' preoperatively poor condition Stricture and abscess formation associated with indwelling ureterostomy catheters have become more common the longer the follow-up Occasional calculi have developed Ureterostomy cups without catheters seem better than catheters for avoiding these complications but only a few patients can and will manage them At the best, the patient must wear a cumbersome and untidy apparatus, and at the worst, the patient will be physically miserable and socially unacceptable If the ureters are transplanted to the bowel above a normal anal sphincter the patient does not need apparatus, is socially acceptable, and except for the necessity of sitting to urinate, which half the population does naturally, appears outwardly normal However, the problem is not simple because the immediate and late risks of uretero-intestinal anastomosis are not only greater but are usually of more grave importance than after skin transplantation We have transplanted the ureters to the bowel on 104 patients by the Coffey I intraperitoneal method Thirteen deaths resulted, a mortality of 12 5 per cent Two patients died of peritonitis from leakage and 1 from small intestinal obstruction at the operative site This 2 8 per cent represents the only postoperative mortality due to complications in the peritoneum, the urinary tract, or the gastro-intestinal tract. Of the remaining 10 deaths, 3 died of congestive cardiac failure, 3 of embolism, 3 of carcinomatosis and 1 from the effects of a radical operation on a recurrent urethral carcinoma. We would emphasize the fact that this series includes palliative cases and that only 8 patients had transplantation for conditions other than neoplasm. The oldest patient was 82, and 7 were in their seventies. Thirty-three, including the 13 just mentioned, are known now to be dead and 71 are living from 1 to 56 months. Temporary nephrostomy was necessary on 3 patients and one other is now carrying nephrostomy tubes during convalescence from cystectomy. One nephrectomy has been necessary. One ureter was successfully implanted into the bowel a second time. Three patients have had one or both ureters transferred from the bowel to the skin because of poorly functioning uretero-intestinal anastomoses. In brief, of the 207 ureters transplanted to the bowel 26 were unsuccessful because of the postoperative death of the patient, one is unsuccessful as nephrectomy has become necessary, 5 are failures because the ureter was necessarily transferred to the skin, and 2 at this time must be called failures because the patient is wearing bilateral nephrostomy tubes. The second implantation of one ureter is only a partial failure as the second attempt remains successful over a year later. Thus, of 207 transplants 34 were immediate failures but 173, or 84 per cent were early successes.

When we first began this series of Coffey I transplants we were more concerned over the possibility of leakage with peritonitis than over the possibility of significant hydronephrosis. As just pointed out, only 2 of 104 patients have had leakage and peritonitis so that this has not been the prime problem that we had anticipated. Hydronephrosis, however, is of major consideration. In general, infection in these kidneys is dependent mainly on obstruction. Those patients with marked hydronephrosis are more susceptible to pyelonephritis and the pyelonephritis is more severe than in patients with no dilation. Acute febrile episodes of renal infection have not been common and most have been mild. One patient died of periartritis nodosa 11 months after transplantation, at which time there was no hydronephrosis on either side as evidenced by intravenous pyelograms shortly before death and also by autopsy. At postmortem examination the pelvic urines were grossly clear and contained only occasional white cells in a centrifuged specimen. The culture of pelvic urine on one side was sterile and on the other a few colonies of pyocyaneus grew out in 72 hours. Too much inference cannot be drawn from one case such as this, but clinical and experimental evidence also indicates that the less obstruction, the less is the problem of infection. Dr. Scott Gardner and I reviewed our first 39 cases in considerable detail and on the basis of intravenous pyelograms we classified 48 per cent as good, 39 per cent as intermediate and 13 per cent as poor. Probably 15 per cent of our transplants show no traces of hydronephrosis, but we still do not have the key to the problem as a review of these excellent cases has not found a common denominator not also present in less successful cases, though no doubt the denominator is there! A mild hydronephrosis has been the rule, grade 1 on the basis of 0 to 4, and patients seem to tolerate this without difficulty. Our subsequent cases have shown a definite improvement over this which we suspect is due to several, apparently minor, improvements in operative technique. We no longer dissect the ureter upwards beyond what is just necessary to allow it a lax and smooth course into the bowel. Great pains are taken not to injure the ureteral wall, especially by leaving adventitial tissue attached. The flaps of the trough in the bowel wall are widely raised and all circular muscle is completely divided to prevent pressure on the ureter later placed in the trough. The incision through the mucosa is now made liberally and transversely instead of a tiny nick which might constrict the ureter passing through (an idea derived from Davalos). The mucosal incision is now seldom less than 1½ cm. Finally every effort is made to suture the trough over the ureter loosely and especially not to make the suture lines so long as to constrict the ureter at its entrance into the bowel incision. In fact, after all suturing is completed a regular sized Kelly clamp can be passed beside the ureter without putting tension on the sutures. We have not stressed speed, believing that each step requires judgment and attention to several details. This includes the work of 11 operators and only one had had any previous experience with ureterosigmoidostomy. Perhaps our average time for a bilateral transplantation is 3½ hours. The majority had bilateral transplantation at the same operation. Reabsorption of urine from the rectum seems theoretically possible and does occur to a minor extent in some patients but the cause of uremia, in our experience, has never been due to this as the main cause, but it must be remembered that these ureters were all implanted in the sigmoid or rectum. We have transplanted in dogs the right ureter into the cecum, then done a left nephrectomy, and observed the development of uremia even though the transplant functioned beautifully. Still further, a cecostomy has relieved this uremia. Incidentally, this is one of the few ways of producing uremia with nearly normal renal function. Two patients have formed calculi but one had formed calculi before transplantation also. More calculi have formed in the ureterocutaneous transplant cases using catheters. The patients with bowel transplants void every 3 or 4 hours in the day and once or twice at night. Occasional patients void more frequently, especially those who received x-radiation, and occasional patients, less frequently. One patient voids 2–3 times a day, none at night, and has excellent pyelograms and a normal blood urea nitrogen over a year after operation. Some adjustment seems necessary as many patients had mild to moderate frequency for 1 to 2 months postoperatively. Occasionally hemorrhoids which were previously only a little bothersome became troublesome after operation but this has not been a great problem nor has hemorrhoidectomy yet been done. All anal sphincters seemed to function well before transplantation and those in whom there was any doubt were tested with enemas. All functioned well postoperatively and none needed to wear protection for the clothes, though 3 sphincters which were mechanically injured at subsequent operations did not retain fluid well after the injury. The long-term prognosis is most difficult to determine, and most especially so because most deaths have occurred from cancer, not renal disease. A case which is quite satisfactory in regard to the transplants 6 months after operation seems to have a good prognosis in that regard for another few years at least. Many pyelograms improve during the first 3 to 4 months, apparently as edema and nduration subside. In the relatively brief time of our follow-up it has been rare for good pyelograms at 4 months to become bad, unless cancer is the cause. Many patients with intermediate degrees of hydronephrosis are doing quite well 1 and 2 years later. Those with marked hydronephrosis, especially on both sides, certainly have a guarded prognosis and we have debated whether further surgical correction is not warranted when all spontaneous improvement has ceased and no cancer is evident.

As previously mentioned, only 2 deaths occurred in the hospital after over 77 total cystectomies for cancer. One death was due to pulmonary collapse immediately postoperative and the other to paralysis in a palliative case. We prefer the perineal abdominal approach except in rare special instances or in occasional females where the procedure may be quite satisfactorily done through the vagina. The prostate and seminal vesicles are dissected free of all structures except the bladder, after the classical method of Young. Two drains are placed into the pelvis, the prostate pushed inside, and the perineum closed with the two drains coming out on one side of the incision. The bladder is now approached suprapubically and the so-called pedicles are approached either by holding the prostate upwards and dissecting beneath on either side, or more often the dissection proceeds down the posterior aspect of the bladder. The peritoneum is usually intentionally opened and the patch most adherent to the bladder is removed with the specimen. The peritoneum is closed, though in one instance so much peritoneum was removed that a gutta percha dam had to be used and left in for ten days because closure was impossible. The wound is irrigated and one suprapubic drain left through the multi-layer closure of the abdominal wall. It is only very rarely necessary to leave packing to control hemorrhage. This operation is not performed in a hurry and our operative time probably averages 2½ hours. A mild degree of wound infection is the rule but the dependent perineal drainage seems to care for this adequately. The suprapubic drain is put in mainly to have a tract to insert a catheter for irrigations if infection becomes notable. The suprapubic drain is removed usually on the second postoperative day. One perineae drain is removed on the third or fourth postoperative day, and the last on the eighth or ninth. To the best of our knowledge 22 of the 77 patients are dead; 55, or 71 per cent, are still alive from 1 to 68 months. Three patients, 2 with grade 3 carcinoma and 1 with adenocarcinoma, are living without evidence of cancer beyond the 5 year anniversary of diagnosis, but the vast majority were done less than 5 years ago.

Radiation seems to produce 15 to 20 per cent 5 year survival and about 6 per cent cures without avoiding, and probably adding to, a marked morbidity rate. Without any treatment about 10 per cent survive 5 years, and none are cured and though no morbidity is avoided, none is added. Of the general population of that age, 88 per cent survive 5 years. With the situation this bad an attempt at some other promising therapy seems warranted. Local destruction of malignant bladder tumors, exclusive of papilloma, produced such poor results as to label the method not promising, though some temporary palliative benefits were evident. Bladder resection had a mortality nearly as high as uretero-intestinal transplantation without showing the same promise or producing as much palliation. On the other hand highly selected cases have done very well with bladder resection but the method is not so widely applicable as cystectomy. Ureterocutaneous transplantation carries a low mortality and a high, though usually not critical, morbidity. The comfort and social status of patients with ureterocutaneous anastomosis are, with occasional exceptions, best described as "messy". Although it may be true, it is not yet evident in this relatively recent series that the longevity of the patient with average ureterocutaneous anastomoses is greater than the longevity of the patient with average uretero-intestinal transplants. Uretero-intestinal transplantation in our hands by the Coffey I method carries a 12.5 per cent mortality, though only 2.7 per cent died of local complications. Approximately 75 per cent had an entirely satisfactory postoperative course. Thirty-one per cent of 104 (96 with neoplasm) patients having Coffey I transplants are known dead and 69 per cent survive from 1 to nearly 60 months. Approximately $\frac{1}{2}$, or a little more, have done extremely well from the time of operation to the time of this tabulation in regard to the transplantation; about $\frac{1}{4}$ have had mild troubles including poor pyelograms or elevated blood urea's even when asymptomatic; $\frac{1}{8}$ have had major severe complications; and $\frac{1}{8}$ died of complications. The palliative effect has been impressive and partly on this account we have not limited our selections of patients to good risks or to potentially curable situations. These patients' comfort and social status can be described as quite satisfactory.

Total cystectomy carries a fairly low mortality of 2.7 per cent; major complications following this procedure are uncommon and usually not specific for cystectomy except, of course, the recurrence or persistence of cancer. Considerable palliation is accomplished. The average survival of 11 purely palliative or heroic cases was 15.2 months. With 3 of these 11 living over 3 years and 3 still alive, this compares well with the 18.8 month average of untreated cases when one remembers that the status of these 11 was considered hopeless at the onset of treatment. Three cystectomized patients with "full blown" malignant bladder tumors already survive over 5 years without evidence of cancer, whereas it would be difficult to hand-pick a series of 77 radiation treated cases containing three "5 year cures" of grade 3 lesions from the whole 500 radiation records reviewed by this speaker.

Lest I be misunderstood, I should like to make a few closing remarks. It is possible for radiation to cure bladder cancer and if for no other reason, radiation cannot therefore be totally abandoned in this pitiful bladder cancer situation. Radiation as a palliative measure against metastases is very valuable. We have not proven beyond peradventure that surgery cures more bladder cancer than radiation. We do feel that uretero-intestinal anastomosis and total cystectomy is a formidable undertaking even for well trained surgeons.

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AN ARTIFICIAL SPHINCTER: A NEW DEVICE AND OPERATION FOR CONTROL OF ENURESIS AND URINARY INCONTINENCE[1]

FREDERIC E. B. FOLEY

GENERAL CONSIDERATIONS

Involuntary escape of urine is a dreadful affliction. The escape of urine may occur through an external urinary fistula or through the intact urethra.

With an external urinary fistula, urine escapes through an abnormal communication between the urinary passages and the body surface made by trauma, disease or surgical interference. This presentation is not concerned with urinary fistula.

Involuntary escape of urine through the intact urethra occurs as enuresis and as incontinence. With enuresis there is an anatomically and neurologically intact sphincter and the involuntary escape of urine is caused by a functional and usually temporary disturbance of innervation. The commonest form of enuresis is the nocturnal enuresis of childhood.

Incontinence of urine occurs as paradoxical or overflow incontinence and as true incontinence.

Overflow incontinence is caused by vesical neck obstruction or by a disturbance of innervation marked by spastic contraction of the vesical or urethral sphincter causing complete retention of urine. The bladder is always full to capacity. Urine excreted into the bladder in excess of its capacity is forced through the obstructed vesical neck or spastic sphincter to escape involuntarily.

This presentation is not concerned with overflow incontinence.

In true incontinence there is escape of urine through an anatomically or neurologically incompetent sphincter. With complete incontinence the bladder is always empty. With incomplete incontinence the bladder partially fills, urine excreted into the bladder in excess of "continent capacity" is not retained and escapes through the urethra.

Anatomic incompetence of the urethral sphincter is usually the result of trauma: obstetric, surgical or otherwise. Neurogenic incompetence of the sphincter is due to organic central nervous system disease, injury or anomaly causing permanent relaxation of the external sphincter. In females incontinence may be caused by "idiopathic" relaxation of the sphincter not of traumatic or neurogenic origin.

Distinction must be made between correction or cure of enuresis and incontinence, and care or control of these conditions. The subject presented does not deal with correction or cure, but only with care and control.

The measures employed by pediatricians and neuropsychiatrists for cure of nocturnal and other forms of enuresis are not generally successful. Trial of such treatment is warranted but its accomplishment is limited. Suffice it to say that despite such treatment the conditions persist to the age of puberty in a very large number of cases and into adult life in a substantial number of cases, as witnessed in the armed services

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[1] Read at annual meeting, American Urological Association, Cincinnati, O., July 26, 1946 and the Urological Section of the American Medical Association, San Francisco, Calif., July 6, 1946.

Neurosurgical accomplishment in the correction of incontinence due to disturbed innervation is extremely limited Most central nervous system lesions causing urinary incontinence are not amenable to surgical correction Only a rare case of neurogenic incontinence is capable of surgical relief So correction of incontinence by neurosurgery plays a small part in the clinical problem

Urologic and gynecologic surgeons have much to offer in the correction of incontinence in the female caused by anatomic damage to the urethral sphincter or its "idiopathic" relaxation The Kelly plication operation and other procedures directed to the same anatomic purpose are successful in a substantial proportion of cases

Surgery has little or nothing to offer for correction of incontinence in the male due to an anatomically damaged external sphincter The writer's attempts in this direction have been complete failures Plication of the male sphincter within the triangular ligament in a way similar to the plication operation on the female urethra just does not work Transplantation of the Gracilis muscle and other blue printed tricks are usually not successful, or at least they require an anomalous degree of surgical skill

The shortcomings of pediatricians and neuropsychiatrists in correcting enuresis and the failure of surgical effort to cure incontinence in the male, and the writer's disillusionment in these pursuits, stimulated an effort in the direction of improving care and control of these conditions

All previous means of caring for enuresis and incontinence have been makeshifts and far from satisfactory The method presented here is likewise a makeshift but appears to be vastly more satisfactory and convenient than its makeshift predecessors

The previous means of caring for incontinence and enuresis have been·

1) Suicide
2) Social ostracism
3) Wearable urinal
4) Retention catheter
    a) External retention,
    b) Internal (self) rentention
        1 Pezzer catheter
        2 Malecot catheter
        3 Foley bag catheter
5) Diversion of urinary flow
    a) Cystostomy
    b) Ureterostomy
    c) Nephrostomy
    d) Ureterosigmoidostomy
6) Cunningham incontinence clamp

Inclusion of suicide and social ostracism is not facetious

The wearable urinal, rubber urinal, has been used extensively. Its bother, irritation, unsanitariness and dissatisfaction are too well known for its shortcomings to need elaboration.

Indwelling catheter drainage has been used considerably. The catheter may be held in place by external fixation with adhesive tape or other means. Escape of urine around the catheter is the rule if bladder filling with interval emptying of the bladder is attempted. Whatever means of external fixation is employed it needs constant attention and is extremely troublesome. Moreover, such a catheter does not always accomplish its purpose. There may be escape of urine around the catheter even when interval emptying of the bladder is not employed and constant drainage through the catheter is permitted.

Other forms of catheter provide for internal fixation, the so-called self-retaining catheter. The old forms of self-retaining catheter are the Pezzer or mushroom tip catheter and Malecot or wing tip catheter. Both of them, particularly the Pezzer catheter, are not easy to introduce and neither of them is securely self-retaining. The most recent form of self-retaining catheter, the so-called Foley bag catheter, does actually retain itself with reliable security. It is a makeshift means of caring for incontinence which has not been fully appreciated. The distended bag in the vesical neck usually prevents leakage. In many cases the Foley bag catheter can be employed for control of incontinence with substantial satisfaction to both patient and physician and should be used more extensively for this purpose.

Diversion of the urine by surgical means is a makeshift means of caring for incontinence. This is accomplished by cystostomy, ureterostomy, nephrostomy or ureterosigmoidostomy. With the exception of ureterosigmoidostomy all of these merely convert escape of urine through the urethra into escape of urine through an external urinary fistula. The latter may be more easily cared for than urethral incontinence but the improvement is not much.

In recent years the Cunningham incontinence clamp has been used extensively. Since the advent of transurethral resection this extremely useful device has found its place in the sun. It is not usable in the female. Perineal prostatectomy and transurethral resection have made it well-nigh indispensable for use in males.

Despite its usefulness the objectionable features of the Cunningham clamp are obvious and cannot be denied. Many patients do not tolerate it at all. It is cumbersome and uncomfortable. One of its chief objections is the engorgement and partial erection which occur distal to the site of application. No worthy contribution such as the Cunningham clamp can be belittled by improvement. That is not the intention in mentioning its shortcomings as preface to presentation of an improvement.

Control of incontinence in the new way here presented is accomplished by a very simple mechanical device which functions pneumatically. The device has been called "*An Artificial Sphincter*". It is applied to the urethra which is compressed by air to prevent escape of urine.

The artificial sphincter may be applied to the urethra in its normal anatomic relationships or to a segment of urethra surgically isolated from adjacent structures by a new operation which has been called a "Cutaneous Tunnel Operation".

THE ARTIFICIAL SPHINCTER

The artificial sphincter consists of a pneumatic or inflatable incontinence clamp (fig. 1, *A*) which compresses and occludes the urethra, and an inflating device (fig. 1, *B*) communicating with it by means of an air passage of rubber tubing. The device is carried in the trouser's pocket.

The illustrations figures 1, 2, 3, and 4 and their captions describe clearly the construction, function and application of the artificial sphincter, pneumatic incontinence clamp and inflating device. No further description of them is required.

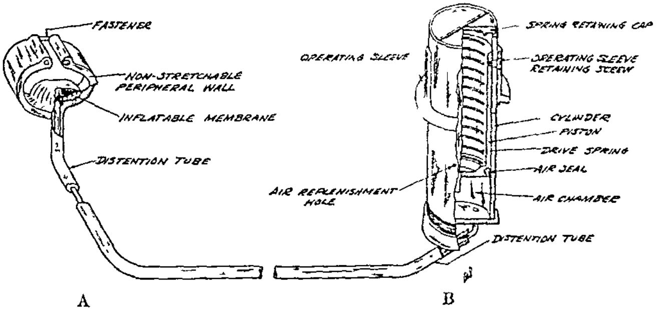

FIG. 1. Artificial sphincter. *A*, [illegible] *B*, inflating device. Pneumatic incontinence clamp consis[illegible] flatable inner surface. Ends of ring are fastened together to [illegible] urethra (fig. 3, *A* and *B*) or a segment of urethra isolated by cutaneous t[illegible] or external wall of ring, *A*, is non-stretchable. On [illegible] rubber. Between peripheral wall and inner memb[illegible] ter from catheter [illegible] ting device is in form of a piston-cylinder assembly [illegible] Piston is hollow and accommodates a drive spring. Spring activated piston [illegible] of cylinder (fig. 2, *A*) to inflate pneumatic incontinence clamp. An external sleeve inwardly fixed to piston permits retraction of piston with displacement of air back into cylinder and deflation of clamp (fig. 2, *B*).

THE CUTANEOUS TUNNEL OPERATION

The purpose of the cutaneous tunnel operation is to permit application of the pneumatic incontinence clamp to an isolated segment of urethra without encirclement and constriction of the rest of the organ, particularly the cavernous bodies, to the end of avoiding engorgement and partial erection distal to the site of application. This form of application permits maximal effectiveness in occluding the urethra by a clamp of minimal size requiring the smallest possible displacement of air.

A segment of urethra about 4 cm. in length extending forward from the penoscrotal junction, and surrounded by its corpus spongiosum, is separated from the other structures of the penis by a cutaneous tunnel.

The masterful drawings of Mr. William P. Didusch, with their abundant labelling (figs. 5 and 6) illustrate the procedure so clearly that only "precautions" need be added to make clear all details of the operation:

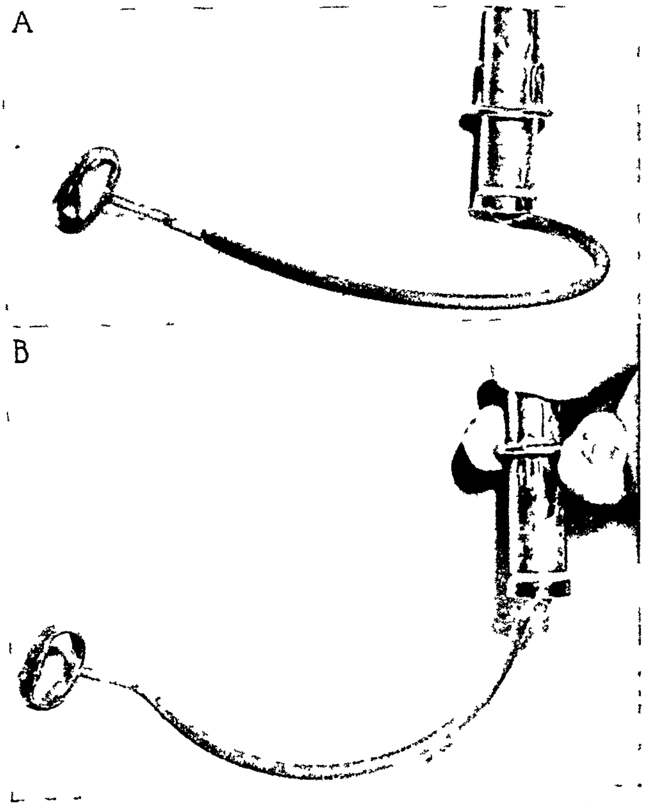

FIG. 2. *A*, pneumatic incontinence clamp inflated; *B*, pneumatic incontinence clamp deflated.

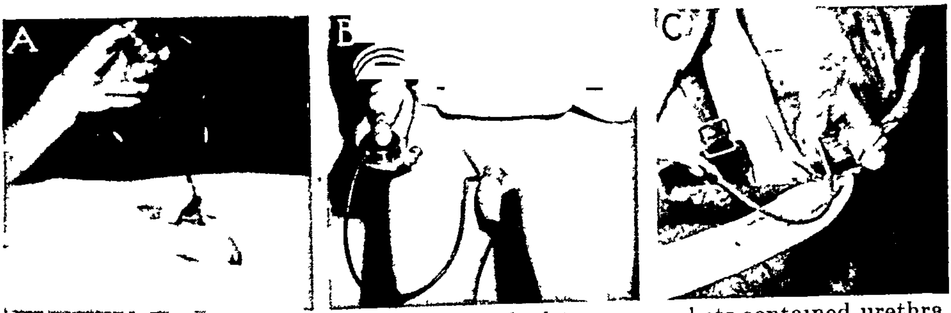

FIG 3 *A*, pneumatic incontinence clamp applied to penis and its contained urethra for control of nocturnal enuresis. *B*, pneumatic incontinence clamp applied to penis and its contained urethra for control of incontinence caused by spina bifida with hydrocephalus and paraplegia *C*, pneumatic incontinence clamp applied to a segment of urethra isolated by cutaneous tunnel operation for control of permanent incontinence in an adult caused by transurethral prostatic resection.

1) While the skin incisions are made and during division of the attachments between the corpus spongiosum and the cavernous bodies the urethra and flaccid corpus spongiosum should be supported by the largest sound introducible into the urethra. For this a generous meatotomy slit should be made, if need be.

To have the urethra and corpus spongiosum thus stretched taut over the sound greatly facilitates the dissection. The penis is stretched forward over the sound by a towel clip applied to the glans penis.

2) The skin incisions and cutaneous tunnel as originally made should be at least half again as long as the tunnel is to be after healing. Cicatrization of the repair process greatly shortens the original surgically made opening. Accordingly, an eventual isolated segment of urethra 4 centimeters long requires skin incisions at least 6 centimeters long.

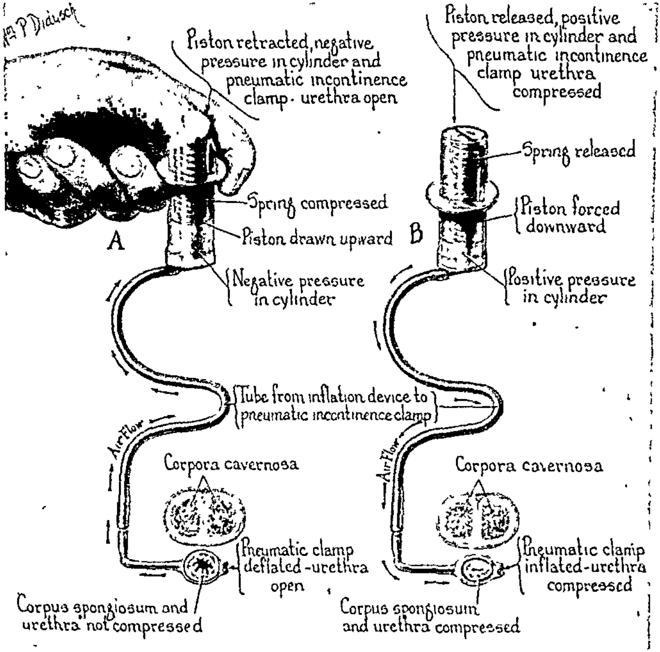
W. P. Didusch
Piston retracted, negative pressure in cylinder and pneumatic incontinence clamp - urethra open
Piston released, positive pressure in cylinder and pneumatic incontinence clamp urethra compressed
Spring released
Spring compressed
Piston forced downward
A
Piston drawn upward
B
Negative pressure in cylinder
Positive pressure in cylinder
Tube from inflation device to pneumatic incontinence clamp
Air Flow
Air Flow
Corpora cavernosa
Corpora cavernosa
Pneumatic clamp deflated - urethra open
Pneumatic clamp inflated - urethra compressed
Corpus spongiosum and urethra not compressed
Corpus spongiosum and urethra compressed

FIG. 1. Schematic drawing, showing operation of artificial sphincter applied to segment of urethra isolated by cutaneous tunnel operation.

3) The skin incisions should be placed farther toward the dorsum than at first sight might seem appropriate. This precaution will give sufficient skin to permit approximation of the ventral edges of the incisions around the urethra and corpus spongiosum without tension—which is most important.

4) It is desirable not to enter the venous spaces of either the corpus spongiosum or corpora cavernosa. This is not always avoided. The resulting venous bleeding is readily controlled by a transfixed ligature of 000 plain catgut.

5) The skin edges are approximated with interrupted sutures of 000 plain

catgut. Postoperative removal of non-absorbable sutures is troublesome and their use is not to good purpose.

6) There may be temptation to approximate by suture the edges of Buck's fascia either by a separate line of sutures or by inclusion of the fascia in the skin sutures. This should be carefully avoided. The sutures should embrace only the skin without inclusion of either Buck's fascia or areolar tissue. Small vessels in the latter structures are important to good healing and their occlusion by suture should be avoided.

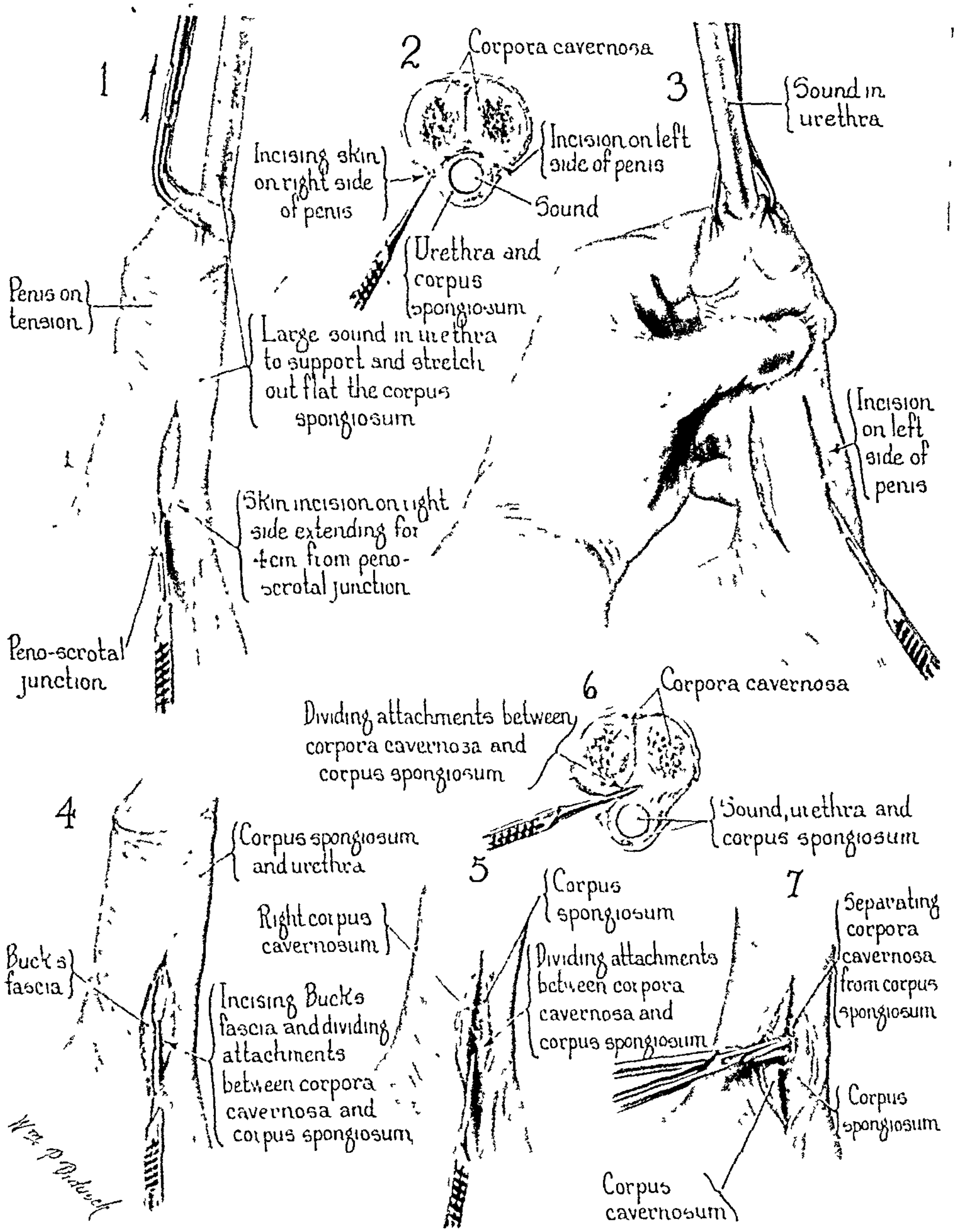
1
Penis on tension
Large sound in urethra to support and stretch out flat the corpus spongiosum
Skin incision on right side extending for 4 cm from peno-scrotal junction
Peno-scrotal junction
2
Corpora cavernosa
Incising skin on right side of penis
Incision on left side of penis
Sound
Urethra and corpus spongiosum
3
Sound in urethra
Incision on left side of penis
6
Corpora cavernosa
Dividing attachments between corpora cavernosa and corpus spongiosum
Sound, urethra and corpus spongiosum
4
Corpus spongiosum and urethra
Buck's fascia
Right corpus cavernosum
Incising Buck's fascia and dividing attachments between corpora cavernosa and corpus spongiosum
5
Corpus spongiosum
Dividing attachments between corpora cavernosa and corpus spongiosum
7
Separating corpora cavernosa from corpus spongiosum
Corpus spongiosum
Corpus cavernosum

FIG 5. Cutaneous tunnel operation. For details of technique of operation, see text.

8) To avoid wetting of the site of operation an indwelling catheter is installed. This should be of minimal size in order not to add tension to the suture line. An F 16 5cc bag Foley self-retaining catheter is best suited to the purpose.

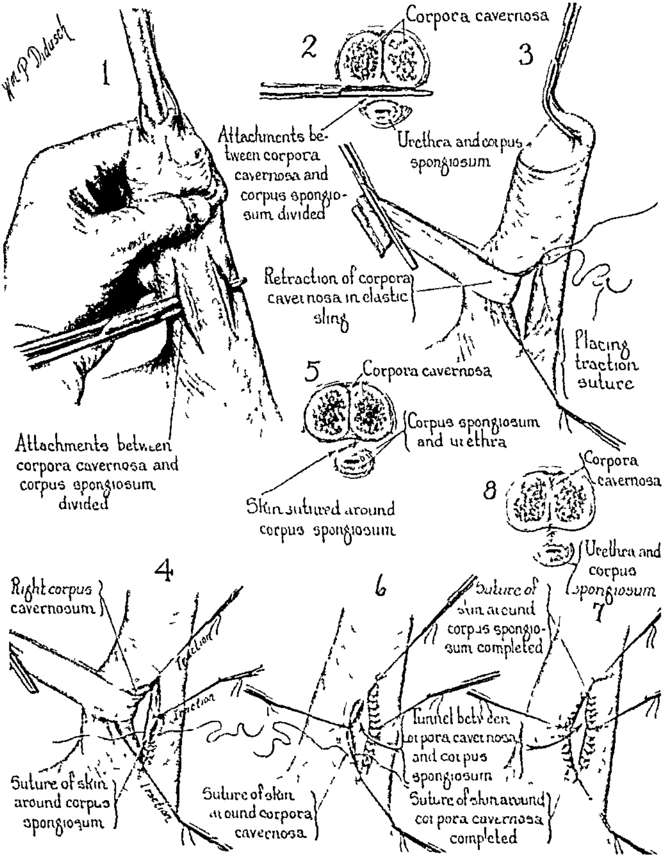
Wm P Didusch
1
2
Corpora cavernosa
3
Attachments between corpora cavernosa and corpus spongiosum divided
Urethra and corpus spongiosum
Retraction of corpora cavernosa in elastic sling
Placing traction suture
5
Corpora cavernosa
Corpus spongiosum and urethra
Attachments between corpora cavernosa and corpus spongiosum divided
Corpora cavernosa
8
Skin sutured around corpus spongiosum
Urethra and corpus spongiosum
4
Right corpus cavernosum
6
Suture of skin around corpus spongiosum completed
7
Traction
Traction
Tunnel between corpora cavernosa and corpus spongiosum
Suture of skin around corpus spongiosum
Traction
Suture of skin around corpora cavernosa
Suture of skin around corpora cavernosa completed

FIG. 6. Cutaneous tunnel operation For details of technique of operation, see text.

9) The tunnel and suture lines are covered with penicillin ointment and no dressing is applied.

COMMENT

Any case in which use of the artificial sphincter is contemplated should be carefully appraised.

In the first place it must be determined that the particular case of enuresis or incontinence under consideration is of a sort in which use of the device promises benefit.

Careful inquiry should be made into all details of how the ailment developed. With the facts of the history as a lead there should follow an examination calculated to determine the precise nature of the "enuric" or "incontinent" disturbance. From these indications will be found for or against use of the device and for or against the tunnel operation.

Of paramount importance in the examination is determination of how much if any residual urine there may be.

Of next importance is determination of "tolerable" bladder capacity.

In a general way it may be said that use of the artificial sphincter is contraindicated in:

1) *Overflow incontinence, definitely.*

2) Urgency to the point of incontinence (as distinguished from true incontinence).

3) Contracted bladder without useful capacity (100 cc or less).

4) Disturbance of innervation accompanied by satisfactorily functioning automatic bladder.

Use of the artificial sphincter is indicated in:

1) Juvenile or adult nocturnal enuresis and perhaps in some cases of diurnal enuresis.

2) Disturbances of innervation marked by true incontinence and not accompanied by vesical spasticity to the point of non-useful bladder capacity (less than 100 cc).

3) Postoperative incontinence accompanied by useful bladder capacity (100 cc or more).

It has been suggested that cases of spinal cord injury marked by complete retention with overflow (paradoxical) incontinence be converted into true incontinence by transurethral destruction of the spastic sphincters followed by application of the artificial sphincter. The writer has had no experience with this application of the device.

In the young boy with not fully grown penis or in the older individual with abnormally small penis the pneumatic incontinence clamp is best applied to the whole circumference of the penis without separation of the urethra by the cutaneous tunnel operation. This form of application (fig. 2, *A* and *B*) is particularly appropriate in cases of juvenile enuresis. With permanent incontinence, like that of spina bifida, the pneumatic incontinence clamp should be applied to the whole circumference of the penis during childhood and continued until size of the penis makes isolation of the urethra by the cutaneous tunnel operation feasible and to good purpose.

Even in the adult with fully developed penis but with only temporary incontinence the clamp may be applied to the intact penis. In the adult this form of application is not so effective and trouble free as application to an isolated segment of urethra (fig. 3, *C* and fig. 4). Only in cases of incontinence definitely known to be permanent should there be resort to the cutaneous tunnel operation.

The cutaneous tunnel operation is contraindicated in:

1) Enuresis or incontinence not definitely known to be permanent.

2) In cases of penis, child or adult, so small that the procedure is not properly feasible and is incapable of giving an isolated segment of urethra of proportions suitable for application of the pneumatic incontinence clamp.

The cutaneous tunnel operation is indicated in:

1) Adult nocturnal enuresis proved to be permanent in which application of the pneumatic incontinence clamp to the whole circumference of the penis is not well borne becuase of discomfort or the disturbance caused by engorgement and partial erection distal to the site of application.

2) Permanent incontinence accompanied by useful bladder capacity and a penis of size making the procedure properly feasible.

While the cutaneous tunnel operation has been employed only in males a similar procedure in females, formation of a mucosal tunnel by incisions in the anterior vaginal wall and almost identical isolation of the urethra between vesical neck and external meatus, would appear to be anatomically feasible.

It should be pointed out that in a substantial proportion of cases of nocturnal enuresis use of the artificial sphincter over a period of a few weeks will be followed by disappearance of the "bed wetting" and ending the need for artificial control. An identical observation was made by O'Conor[2] in connection with the control of enuresis by the Cunningham clamp.

Under the writer's direct supervision the artificial sphincter as here described has been used with substantial satisfaction in many cases of enuresis and incontinence. However, it is not felt that the present forms of either the pneumatic incontinence clamp or the inflating device leave nothing to be desired or that they are yet sufficiently well perfected to be offered for general use. Effort in this direction is proceeding with the invaluable aid and co-operation of Frederick C. Wallace of American Cystoscope Makers, Inc., through whom the device will be made available.

In addition to the above acknowledgment of Mr. Wallace's contribution to the problem, acknowledgement is made of the cooperation and assistance rendered in the past by Mr. George Winder formerly of American Anode.

228 Lowry Medical Arts Bldg., St. Paul, Minn.

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[2] O'Conor, Vincent J.: Urologists Correspondence Club Letter, October 12, 1942.

ACUTE EXUDATIVE CYSTITIS OF UNDETERMINED ETIOLOGY[1]

J. V. BERRY AND N. E. BERRY

The purpose of this communication is to call attention to the importance of a more general knowledge of the pyurias of unknown etiology variously described as acute exudative cystitis, acute interstitial cystitis, acute hemorrhagic cystitis, amicrobic pyuria and Reiter's disease.

Papers have appeared on the subject by Cook, Moore, Colby, Briggs, Sargent, and others, but there are an appreciable number of urologists who have never recognized a case. Many medical officers attached to urological services can recall having seen cases that probably belonged to this group which were not recognized as such because the officers were not familiar with the syndrome. The characteristic feature of the condition is a history of non-specific urethritis of variable duration, followed by an acute hemorrhagic cystitis. The acute onset of frequency and strangury, the profuse hematuria and the absence of loin pain and febrile reaction characterize this syndrome from most other infections of the urinary tract. Admittedly the cystitis is only part of the picture, but it is a most distressing one and considering its protracted course, if not recognized may become a serious debilitating disease.

In Reiter's syndrome, conjunctivitis and arthritis are also present. It might be argued that this syndrome is a separate entity, but it has so much in common with the other group of cases that they may properly be discussed together. They all have non-specific urethritis, intense cystitis and sterile urine. Further, they all show dilatation of the upper urinary tract. Reiter observed the syndrome in a young German officer in 1916. Following an acute gastro-intestinal upset the man had a purulent urethral discharge, which was accompanied by an acute conjunctivitis and acute arthritis of the right knee. No gonococci could be demonstrated in the urethral or conjunctival discharges. Three weeks after the onset there was an extension of the arthritis to other joints with an acute febrile reaction. After 2 months of the illness had passed the patient had acute cystitis and recurrent conjunctivitis.

Since Reiter's original publication some 65 cases have been reported (Miller and McIntyre). Lever and Crawford reviewed the first 45 case records and concluded that in some the syndrome was not complete and in others the bacteriological studies were not sufficient to exclude the presence of gonococcic infection. These authors commented that nearly half of the cases were soldiers on active duty in either the first or second World Wars and that only 1 case had been reported in America. Rosenblum and Sargent have each published a series in the past year. They point out that where all the symptoms are not present, the disease may be mistaken for acute prostatitis, acute cystitis and conjunctivitis. Colby has drawn attention to the upper urinary tract complications in Reiter's disease, and we had a similar case in our series.

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[1] Read at annual meeting, Western New York-Ontario Urological Society, Thousand Islands Club, September 11–14, 1946.

Our experience consists of 24 cases, almost all of them soldiers They all had urethritis and all showed the cystoscopic features noted by Hess and Cook Three cases had severe polyarticular arthritis, 4 cases had acute bilateral conjunctivitis, while 1 had acute iritis as the only complication of the urinary tract lesion In 1 case the purpuric vesicular dermatitis, described by Lever and Crawford, developed Of those whose upper urinary tracts were investigated, all showed dilatation some very marked and with recovery this ordinarily, but not always, rapidly improved

Case Reports

Case 1 A 30 year old married soldier, Private S L , had no history of any illness prior to enlistment in April 1943 About June 7, 1944, an acute creamy urethral discharge developed which was negative for gonococci Extramarital sexual contact was denied There was no improvement after a 5 day course of sulfathiazole, and 2 days later bilateral purulent conjunctivitis developed This improved rapidly under treatment with sulfathiazole ointment but 2 weeks later he had an acutely swollen and painful left knee joint, followed by similar involvement of the right knee

He was admitted to a military hospital June 23, 1944, and given sulfadiazene therapy There was still no improvement in either the discharge or the arthritis and on July 1 he had acute pain and swelling of the small joints of both hands The successive joint reactions had caused a gradual febrile response and by July 15 the patient was acutely ill with fever of 102° The sedimentation rate showed a marked rise from 11 to 103 mm and leucocyte count to 20,000 Cultures of urine and joint fluid failed to reveal any organisms The urinary symptoms had continued with such severity that a cystoscope was passed on August 8, 1944 The bladder capacity was about an ounce and distention caused bleeding The mucosa was intensely inflamed and heaped up with an edematous reaction of the whole bladder surface An exudate covered the walls like a spider web There was no evidence of any necrotic tissue present Bladder irrigations were performed on frequent occasions using silver nitrate solutions and argyrol Penicillin was given to the extent of 600,000 units All of these drugs gave little relief

Intravenous urograms revealed a dilatation of the upper tract and a very much contracted bladder (fig 1)

Novarsenobenzol was given in small doses 3 times a week, and after the first week of treatment the bladder symptoms began to clear.

The arthritis improved, but not until a suppurative focus in the tonsils was discovered and subsequently removed did the patient obtain much symptomatic relief He was out of bed on October 15 and discharged from the hospital 2 weeks later

We were able to trace this man after a year's absence and discovered he had a recurrence of conjunctivitis and cystitis of mild duration There was no recurrence of arthritis

Case 2 This 25 year old soldier, Private J X , reported an acute urethral discharge to his medical officer in March 1944. A clinical diagnosis of gonorrhoea was made, although there were no typical gonococci reported in the smears. Treatment with sulfathiazole for 5 days brought about cessation of discharge and he was apparently cured.

Two weeks later he was admitted to a military hospital with a purpuric vesicular dermatitis and treated first with lead lotion and then with sulfathiazole ointment. The dermatitis was improved slightly but not cured. About 1 week after admission to the hospital he began to complain of dysuria and frequency of urination with terminal hematuria. Rectal examination showed a tender and boggy prostate but no appreciable enlargement. Hot sitz baths and diathermy were advised with all urinary symptoms becoming aggravated.

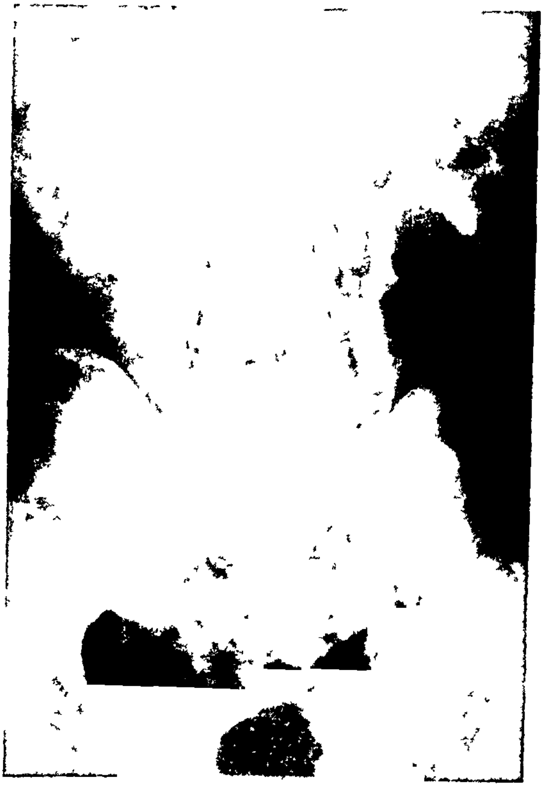

FIG. 1. Case 1. Contracted bladder with dilated upper urinary tract

On June 7, 1944, cystoscopy showed that the bladder was intolerant to more than 2 ounces of fluid. There was intensely acute cystitis with a great deal of adherent exudate. The prostatic urethra, apart from acute congestion, presented no evidence of abscess. The ureteral orifices were not identified because of the marked edema of the trigone.

Throughout this period the dermatitis showed numerous exacerbations and remissions, but at not time did it completely disappear. It was confined mainly to the hands and feet, both dorsal and ventral surfaces being affected, the back of the neck and the shoulder regions. During the latter part of July he had pain and swelling of both hands and feet with a low grade fever, and he began to decline markedly in health. There was a loss of 30 pounds in weight and he showed a marked degree of anemia. Frequency of urination and strangury had become intolerable with gross hematuria. Intravenous urograms showed marked dilatation of both lower ureters and an appreciable dilatation of both renal pelves.

He continued to suffer a good deal; increasing pain in the hands and feet developed, and the left knee and right elbow became involved. This was accompanied by an exacerbation of fever to 101°. On September 1, 1944, he was started on a course of Novarsenobenzol 0.3 gm. and this was repeated 4 days later. Definite improvement followed and his temperature fell to normal. Penicillin was now available and a course of 200,000 units was given with further improvement and he became progressively better. By October 1 his joints and his bladder were virtually normal. This was confirmed by cystoscopy and ureteral catheterization was carried out without obstruction. Pyelograms showed now only a slight dilatation on both sides.

Case 3. A 24 year old, married, Air Force Sergeant, S. T., with 4 years' military service in Canada, reported a purulent urethral discharge to his medical officer on July 1, 1945. There was no history of exposure and the urethritis was reported as non-specific. After 3 weeks' sulfa therapy the discharge became gradually worse and he was admitted to a military hospital for further investigation. On admission to hospital he began to complain of some frequency of urination which rapidly became worse and on July 30 cystoscopy was reported as showing marked cystitis with edema and swelling of the posterior urethra and bladder neck. Bacteriological examination of the urine showed sterile pyuria.

Following the examination he experienced acute pain with frequency every 5 minutes and hematuria so gross that clots retarded the act of urination. The symptoms appeared to improve somewhat in the first course of 900,000 units of penicillin. The relief of symptoms was soon followed by a severe relapse and despite the use of penicillin and sulfa therapy the patient experienced a 3 weeks' period of excruciating pain and frequency.

For the next 3 months the symptoms were almost static with intervals of relief from hematuria and strangury, but with frequency of no less than ½ hourly intervals. During the first week in November acute bilateral epididymitis developed.

On his admission to the London Military Hospital on December 3, 1945, he appeared quite undernourished and pale with considerable loss of weight but not acutely ill. Cystoscopic examination was performed the next day under pentothal anesthesia. A stricture, which barely permitted a 16 F. cystoscope, was detected in the perineal urethra. The bladder capacity was 1½ ounces and the bladder mucosa presented patchy areas of acute inflammation with numerous hemorrhagic areas about the floor and neck of the bladder. The ureteral orifices were swollen and would only admit a 4 F. bougie with difficulty. The orifices were dilated and catheters were passed which revealed clear urine but bilateral hydronephroses (fig. 2, *A*).

December 11, 1945, 0.3 gm. Novarsenobenzol was given for 3 consecutive days with complete relief of hematuria and relief of frequency for 2 hour intervals. After 6 injections the patient took his 2 weeks' Christmas leave and returned with aggravation of symptoms and occasional hematuria. Cystoscopy was repeated, and on this examination the flame-like hemorrhages had disappeared. Over the same areas of the bladder, small blood cysts appeared which on pathological section proved to be *hemangiomata*. On *February 1* (one month later) the hemangiomata had disappeared, leaving numerous small bleeding ulcers with bright hemorrhagic margins.

By the end of February 1946, the patient had received a total of 14 injections of Novarsenobenzol, with relief of his bladder symptoms but with some microscopic hematuria. On March 15, the bladder capacity had reached 3 ounces.

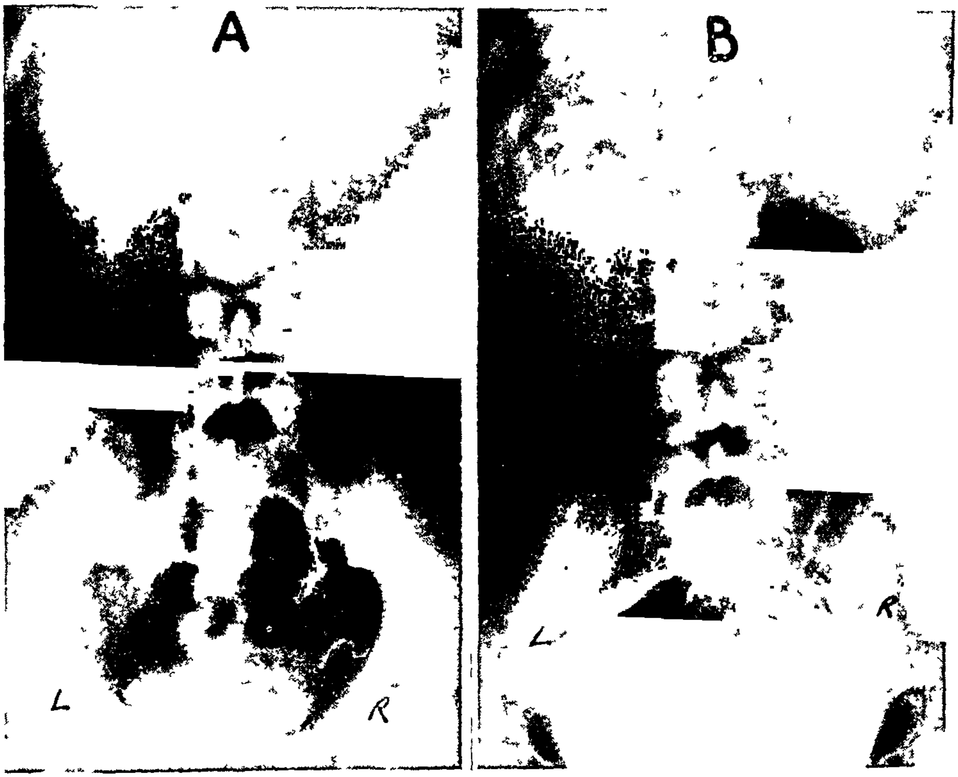

FIG. 2. Case 3. *A*, Dilated upper urinary tract. *B*, After treatment

There were a few small ulcers about the trigone and ureteral orifices appeared quite normal; considerable dilatation of the upper tract however remained. Although this man has recovered from the acute bladder lesion, he has written to me recently to state that his doctor is still giving him periodic dilatations of the bladder. The last intravenous urogram taken on June 12 showed the left renal pelvis normal in size and contour but the right side still showed a mild degree of dilatation (fig. 2, *B*).

ETIOLOGY

The cause of the condition is unknown. A filterable virus has been suggested. It has also been thought to be due to focal infection with toxine in the urine provoking the reaction or that it may be due to a deep-seated coccal infection in the renal parenchyma. It seems to us significant that in all our cases there was antecedent urethritis and, with one exception, this was non-specific. Admittedly, we know little about the cause of non-specific urethritis but there is the possibility that it may be specific, the organism not yet being identified. The *consistently negative smears and cultures in a condition which is obviously* inflammatory can lead only to this conclusion.

DIAGNOSIS

The differential diagnosis concerns the exclusion, first, of gonorrhoeal urethritis and prostatitis, and secondly, tuberculosis. The clinical picture and bladder appearances are highly suggestive of renal tuberculosis. The sterile

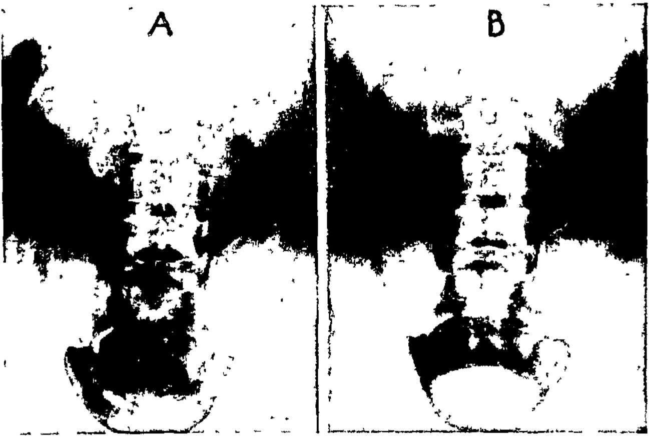

FIG. 3. Contracted bladder with dilated upper tract with whole process reversed in 17 days after institution of specific treatment.

urine adds to the evidence. A diagnosis of tuberculosis should not be made without proof of the presence of tubercle bacilli. One is apt to linger too long under the impression that these cases may be prostatitis, the prostate being exquisitely tender and often presenting a boggy sensation. This is, however, due to the intense cystitis and when properly treated there is not usually any residual prostatic infection. Carcinoma of a diffusely infiltrating type might be a problem to differentiate, but should not be difficult. Familiarity with the syndrome makes the diagnosis obvious. The finding on x-ray of a contracted bladder with dilated ureters and renal pelves is very suggestive of this condition. Characteristically this whole process can be reversed in a short period of time with specific treatment and we believe that such an observation is diagnostic of the disease (fig. 3).

PATHOLOGY

Hess was one of the first to contribute any pathological information on the lesion of acute hemorrhagic cystitis. The early lesion is hemorrhage with mild inflammation of the mucosal stroma. Later vascular channels form in the hemorrhagic areas and finally develop to form hemangiomata. In the terminal stage the mucosa lining the hemangiomata breaks down due to thrombosis, the result of inflammation and scarring, with the formation of punctate ulcers which may appear necrotic but which usually present a hemorrhagic margin. Peters has compared these pathological changes in the bladder typical of the clinical entity known as Hunner's ulcer.

Since no organisms could be demonstrated in the urine, sections of tissue from the bladder were macerated and spread on culture media with negative results. Smears of urethral and conjunctival discharges and joint effusions yielded negative findings. The blood picture was typically secondary hypochromic anemia. The leucocyte response and sedimentation rate was noted to rise and fall in relation to the acuteness of the joint lesions. Apart from some coincidental findings, the laboratory data were of little interest in the whole series.

TREATMENT

The treatment is simplified by correct and early diagnosis, though not all the patients tend to respond in the same way. Local treatment of many kinds has been tried by intermittent and continuous bladder drainage but all were limited by the highly sensitive and intolerant bladders. Mandelic acid and sulfonamides were of little value. Penicillin has not been generally effective but seemed definitely of value in one of our cases. Neoarsphenamine in small doses appeared to be more or less specific and improvement followed its use in all our cases.

General treatment in the nature of nutritious diets, adequate vitamin intake and finally blood transfusions are indicated in the debilitated cases.

Cook had stressed the importance of removing foci of infection.

SUMMARY

A series of 24 cases of acute exudative cystitis is presented, 3 in detail. A few cases were complicated by arthritis, conjunctivitis, iritis and dermatitis.

The acute vesical syndrome is characterized by a profuse abacterial pyuria and gross hematuria. The end result of the inflammatory lesion is a contracted and ulcerated bladder with terminal ureteritis and marked dilatation of the upper urinary tract.

We believe that the condition is caused by an organism, possibly a spirochete and has some relation to non-specific urethritis.

Differential diagnosis concerns the exclusion of gonorrhoea, tuberculosis and malignancy. Familiarity with the symptoms and the urographic findings makes the diagnosis simple.

Characteristically the whole picture can be reversed in a short period of time with specific treatment, the neoarsphenamines being usually employed. Mapharsen, in our experience, is equally efficacious.

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REITER'S SYNDROME: A REPORT OF TWO CASES WITH RESPONSE IN ONE TO LARGE DOSES OF MAPHARSEN

ERNEST N. KHOURY

In the last 2 years attention has been directed to the existence of Reiter's syndrome by the reports of Colby, Bauer and Engleman, Sargent, Lever and Crawford, and Rosenblum. The standard texts in urology fail to mention this syndrome and probably is the reason for the lack of general knowledge of this interesting disease.

SYMPTOMATOLOGY

Reiter's syndrome was first described by Reiter in 1916. Since then 68 cases have been reported in the literature. Until rather recently most of these reports have been in the European literature.

Reiter's syndrome has as a basic triad abacterial urethritis, conjunctivitis, and arthritis. This develops, as a rule, within a few weeks and persistence of any or all of the manifestations has no definite time limit. In addition, ulceration and keratitis of the skin and mucous membranes of the glans and mouth occur.

The genito-urinary manifestations are not limited to the urethra, but go on to cause a diffuse and angry cystitis with marked pyuria and pollakuria. Ureteropyelitis has also been reported.

The conjunctivitis can be quite severe with photophobia, clouding of the cornea and even keratitis.

The arthritis involves more than one joint and can cause severe crippling over a protracted period of time with recrudescence and exacerbations.

The symptoms and signs of the cystitis and pyelitis show a marked similarity to the abacterial pyuria as described by Moore, and Ewarts and Hoffman. It was this similarity in the clinical picture that prompted the author to use heavy doses of Mapharsen in one of the cases reported with dramatic recovery, not only in the urological manifestations, but also in the joint phenomena.

ETIOLOGY

In all of these manifestations there has been a consistent inability to grow on culture or demonstrate in any manner any organisms. Even scrapings of the conjunctiva and biopsy of the synovial sheaths have been fruitless. Reiter reported a spirillum as an etiological agent but no one else has been able to demonstrate the organism. At present the general belief is that it is one of the many virus infections.

Unfortunately, in the cases reported in this paper, facilities for viral studies were not available and none of the recent authors have studied their cases to demonstrate filterable viruses. Future cases should be and undoubtedly will receive the benefit of these studies.

PROGNOSIS AND CLINICAL COURSE

No fatalities from the disease have been reported in the American literature All of the cases reported in the recent literature, however, have had a protracted course, with rather severe optical, joint, epithelial and genito-urinary involvement That this is not the rule in all cases is apparent in this paper In fact, because of the rare recognition of this syndrome, it might well be that it occurs more commonly in milder forms which are completely missed or misdiagnosed

CASE REPORTS

Case 1 J J , a 40 year old white man, was seen in the office with a urethral discharge of 1 week's duration This was associated with burning on urination but no other symptoms The discharge was at first mucoid and later became grossly purulent The patient denied any sexual contact other than with his wife who showed no signs of disease He had taken 90 gr of sulfathiazole daily for 1 week without abatement of the discharge Remainder of the history was not significant

Examination revealed a purulent and abundant urethral discharge The testes and scrotum were normal The prostate was not boggy or tender and had a normal configuration The penis appeared normal except for the discharge, which was purulent and abundant The urethral meatus was small, measuring only 14 F

The 2 glass test showed a cloudy first glass with some shreds in the second glass

A gram stain of the discharge did not reveal any organisms, and wet preparations failed repeatedly to demonstrate any Trichomonas vaginalis

A diagnosis of nonspecific urethritis was made, and a meatotomy done to improve drainage No other treatment was carried out and the discharge gradually cleared up in 10 days One week after the clearing of the urethritis and 17 days after the onset of the urethritis the patient had pain on motion of the left elbow joint There was no swelling or redness of the joint At the same time a mild conjunctivitis developed in the right eye. Both of these cleared up in 1 week on nonspecific therapy

There were no recurrences of these manifestations and the patient has been observed for 2 years in connection with his duties as a physiotherapist

Case 2 G C , a 25 year old office worker, was first seen February 27, 1946 with a chief complaint of profuse urethral discharge of 3 weeks' duration His family physician had given him a 2 weeks' course of sulfathiazole in doses of 60 gr per day without response Smears taken at the onset of the discharge were negative for gonococci and repeated smears showed only pus cells with no evidence of organisms There was a reliable history of no sexual contact other than with his wife who showed no evidence of disease

The general examination was normal The penis appeared normal except for a profuse purulent discharge Smears of this discharge, both by me and a laboratory, showed only numerous pus cells The scrotum and contents were normal. The prostate was boggy and slightly tender. The 2 glass test was cloudy in both glasses.

A diagnosis of nonspecific urethritis was made and treatment with massage and sounds begun with little if any improvement. On March 22, 1946, the bladder was filled with a solution of potassium permanganate 1/10,000 and the prostate massaged. Following this, the patient had marked frequency, hematuria, and cloudy urine loaded with pus cells. The urethral discharge remained the same. On March 30, 1946, in addition to the urethritis and cystitis, bilateral conjunctivitis without photophobia and a swollen and reddened left ankle joint developed. A diagnosis of Reiter's disease was made at this time and the patient was hospitalized.

Three urine cultures of the grossly purulent urine on 3 separate days revealed no growth at any time. A culture of the urine for tubercle bacilli was negative after 2 months. Two chocolate agar cultures of the urethral discharge produced no growth. Chocolate agar cultures of the prostatic secretions on 2 separate days showed no growth.

The urine was persistently alkaline and showed erythrocytes and pus cells with 2 plus albumin.

Urea nitrogen of the blood was 17.2 mgm. per cent.

Erythrocytes were 4.99 million; hemoglobin 15.3 gm.; leukocytes 15,900; polynuclear cells 81 per cent; lymphocytes 7 per cent; monocytes 9 per cent; basophils 3 per cent. The erythrocyte sedimentation rate was 32 mm. per hour. The blood Wassermann was negative.

An intravenous urogram was normal. An x-ray of the left ankle joint on admission showed no changes in the joint configuration. The electrocardiogram was normal.

PROGRESS

The joint was placed at rest without splinting, and the redness and swelling disappeared in 3 days. Slight pain on motion continued, however. The conjunctivitis was never severe and was limited to slight redness of the conjunctiva and sticking together of the lids upon awakening. This cleared up without treatment.

The urethral discharge stopped in 1 week. The marked frequency every half-hour day and night with hematuria persisted and had not cleared up on discharge 9 days later, April 9, 1946.

Cystoscopy showed a diffuse cystitis with marked edema. The trigone and ureteral orifices were obscured by edema.

From April 9 until May 24, the patient was seen at weekly intervals and the urinary symptoms persisted without abatement. The patient found it difficult to sleep and could not work because the knee and ankle joints were stiff and painful on motion. There was no recurrence of the urethritis or conjunctivitis.

On May 24, 1946, almost 3 months after the patient was first seen by me, and 4 months after the onset of urethritis, I decided to start Mapharsen. It was given in 2 weekly injections for 3 weeks, then 1 weekly injection for 4 weeks.

The dose was 06 gm per intravenous injection The response to this therapy was dramatic Three days after the first injection the stiffness in the joints disappeared The urine remained cloudy but the nocturia diminished to 4 times instead of hourly The day frequency diminished to every 2 hours One week after the first injection nocturia was twice and diuria every 2 hours, the urine was less cloudy At the end of the second week the nocturia had disappeared completely and the patient was voiding only 3 or 4 times during the day The urine cleared steadily until on July 1, 1946 the urine showed no pus cells on microscopic examination and was grossly clear Three months after discontinuance of treatment, the urine was still clear and the patient presented no symptoms

COMMENT

As is noted, the first case, while not conclusively proven by negative laboratory work, showed the typical triad and was benign The second case was more completely investigated and may be classed as moderately severe However, it did cause protracted disability The large doses of Mapharsen caused such a rapid and dramatic response that the possibility of a coincidental spontaneous regression cannot be rationally entertained Future cases should have a trial at this form of therapy No attempt is made to explain the pharmacodynamic action in this case

SUMMARY

Two cases of Reiter's disease are added to the 68 previously collected cases It is stressed that possibly many relatively mild cases of this syndrome are missed

A dramatic response to large doses of Mapharsen intravenously is noted in 1 case Previous use of arsenicals by other workers was without response

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SUBACUTE MONOCYTIC LEUKEMIA PRESENTING SYMPTOMS OF PROSTATISM: A CASE REPORT

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The purpose of this paper is to present the second known case of monocytic leukemia in which the presenting symptoms were those of urinary obstruction due to prostatic enlargement.

Monocytic leukemia is no longer a remarkably uncommon condition. Since Schilling first described this condition as a disease entity in 1913, almost 200 cases have been reported in the literature. There has been much controversy as to whether monocytic leukemia is an atypical type of the more common lymphatic and myelogenous forms. However, Evans in 1942 polled 46 hematologists and the consensus of opinion was that monocytic leukemia is a distinct clinical entity.

The pathologic lesions of monocytic leukemia are extremely widespread and eventually nearly all the organs of the body may be invaded by the type cell. Dodge, Black and Mugrage in their case report state that "microscopic findings were not remarkable except for the almost monotonous infiltration by monocytes of every tissue examined." The organs of the genito-urinary system are therefore similarly involved in this disease process. However, it is unusual for the clinical manifestations to first appear within the genito-urinary tract. The usual initial clinical manifestations of the disease being anemia, fatigue, ulcerative gingivitis, when teeth are present, and in many cases cutaneous manifestations. A perusal of the literature reveals only 1 case of monocytic leukemia in which the presenting symptoms were those of prostatic obstruction. This case was reported by Flaherty, Cope and Shecket in 1940. There have been no subsequent reports of this nature.

CASE REPORT

Case No. HH-11009 D. G., a 56 year old white farmer, was admitted to the private urological service of one of us (T.R.F.) in the Jefferson Medical College Hospital on March 18, 1945. The chief complaint was marked frequency of urination of several years' duration.

The family history was negative. The past medical history revealed no confining illnesses other than an appendectomy in 1920. Systemic review revealed that the patient had been having dyspnea on exertion for 6 months. Concomitant with this, he had noticed post-cibum nausea and moderate soreness of his mouth and gums, but no bleeding from the latter. There had been no precordial pain nor dependent edema and the remainder of the review was essentially noncontributory.

The present illness began, approximately, in 1935 when the patient first noticed nocturia and diurnal frequency. This gradually progressed until during the past few years he had had nocturia 2 to 3 times, diurnal frequency every 2 hours, definite diminution in the size and force of the urinary stream, and several episodes of complete urinary retention. During the 6 months prior to admission, the episodes of retention had become so frequent that the patient carried a catheter for self catheterization. The patient had received treatment in the form of occasional bladder irrigations and prostatic massages.

Physical examination revealed a well developed slightly obese white man. The skin was clear. The buccal mucosa was normal. The gingivae were slightly injected, swollen, soft and bled readily, however, there were no ulcerations of the mucosa. There was no cervical, axillary or inguinal lymphadenopathy. The lungs were resonant to percussion and the chest expanded freely and equally bilaterally, however there were a few crepitant rales in both lung bases. The heart sounds were regular and of good quality with no murmurs. The area of cardiac dullness was moderately increased to the left. The liver was not palpable and there was no increase in hepatic dullness. The spleen was not palpable. The remainder of the abdomen was likewise negative with no palpable organs nor masses. The external genitalia were normal except for moderate swelling and tenderness of the right epididymis. The extremities were normal and the reflexes were active and equal bilaterally. Rectal examination revealed a normal anal sphincter. The prostate was greatly enlarged, symmetrical, abnormally tender and of normal consistence except for numerous discrete areas of softness. The fulness of the prostate was particularly noted along the superior borders. There was marked induration of both ampullae and seminal vesicles. On admission, the temperature was 100°F., pulse 94, respirations 22, and the blood pressure 146/90.

The laboratory findings on admission were: Urinalysis: acid, specific gravity 1.015, albumin 4 plus, sugar negative, many leucocytes and erythrocytes, no casts. Hemoglobin 68 per cent, erythrocytes 3.7 million and leucocytes 16,950. A repeat blood count, 12 days after admission, revealed: hemoglobin 52 per cent, erythrocytes 2.6 million and leucocytes 19,200 with a differential count of 34 per cent segmented neutrophiles, 10 per cent non segmented neutrophiles, 18 per cent lymphocytes, 25 per cent monocytes, 6 per cent promonocytes, 7 per cent myeloblasts and a moderate number of microcytes and macrocytes. The prothrombin time was 82 per cent of average normal. The Wassermann and Kahn tests were negative. The blood urea nitrogen was 15.0 mg. per cent. Fasting blood sugar was 91 mg. per cent.

An electrocardiogram revealed low voltage of the T-waves in all leads and was interpreted as indicative of some degree of myocardial impairment.

A plain roentgenogram of the abdomen revealed no masses or abnormal calcifications.

A cholecystogram revealed no evidence of opaque stones nor evidence of a gallbladder shadow and was interpreted as presumptive evidence of impaired function.

Upon admission, the patient was placed on retention catheter drainage. No residual urine was present. Nine days after admission, an attempt to perform a cystoscopic examination was unsuccessful because of marked elongation of the prostatic urethra.

In view of the persistence of fever around 100°F. and the right epididymitis, the patient was given 3 gm. sulfadiazine daily for 7 days with no improvement. At this point, the persistent elevation of temperature and the abnormal blood picture prompted hematological consultation which resulted in a diagnosis of subacute monocytic leukemia. A complete report of the hematologic findings is presented in a subsequent paragraph.

Upon establishment of the diagnosis, the patient was given three 500 cc transfusions of citrated blood at 3 day intervals, large doses of brewer's yeast and penicillin 100,000 units daily.

On the twenty-third day after admission, the patient's condition was deemed satisfactory for a surgical procedure. Under spinal anesthesia, an attempt was made at transurethral electro-resection of the prostate. The surgeon was unable to introduce the resectoscope into the bladder because of the marked elongation of the prostatic urethra and the presence of a massive median lobe. Several cuts were made to secure material for histologic examination and for smears to stain with Wright's stain. Bleeding was profuse. A suprapubic cystostomy was then performed and the bleeding controlled by packing the prostatic urethra. A 34 F. Pezzer catheter was placed in the bladder for drainage and 2 Penrose drains were placed in the prevesical space. The patient received 1000 cc citrated blood during the operative procedure.

The patient's early postoperative course was stormy due to a septic febrile course in which the temperature spiked to 102°F. daily and to refractory ileus. However, the cystostomy wound healed by primary intention and the patient was able to be out of bed by the tenth postoperative day. He received 500 cc citrated blood during his convalescence. The patient became very depressed and "homesick" so that despite a constant fever of 100°F. and generalized debility, it was deemed advisable to permit him to return home. On the day of discharge he had right flank pain and tenderness and it was believed that he was having an episode of pyelonephritis. The patient was discharged on the seventeenth postoperative day after a hospital stay of 41 days.

Subsequent communications from the patient's family informed us that his condition deteriorated rapidly, and he died on May 21, 1945.

It is impossible to state definitely the duration of the disease in this case; however by calculating from the time of exacerbation of his urinary difficulties with the concomitant gingivitis, the duration would appear to be approximately nine months. According to the chronological classification of monocytic leukemia, this case would be of the subacute variety.

Histologic examination of tissue removed by transurethral electro-resection revealed moderate hyperplasia of the prostatic epithelium with marked edema of the stroma and marked round-cell infiltration of the tissue. The exact nature of the round-cells could not be determined from the sections. This difficulty in determining the nature of the infiltrating cells in fixed tissue preparation has been emphasized by Berghausen and Dodge, Black and Mugrage and others (fig. 1).

This case can be presented best from a hematological standpoint by discussing briefly table 1 and figure 2. Table 1 lists the peripheral blood findings.

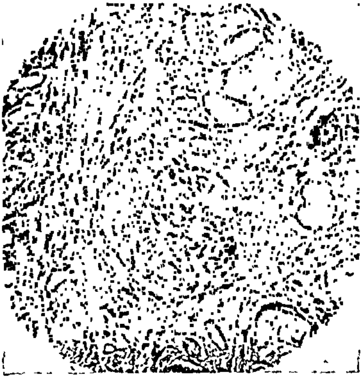

FIG. 1. Section of prostate, showing diffuse infiltration

TABLE 1. *Peripheral blood counts taken during April 1945*

	APRIL			
	3rd	6th	12th	20th
Hemoglobin (%-Klett)	55	54	54	49
Red blood cells (in millions)	2.7	2.5	2.7	2.7
White blood cells (in thousands)	24	18	47	11
Platelets (in thousands)	86	100	34	
Differential (in %)				
Polymorphonuclears	25	13	15	20
Myelocytes	2	7	7	4
Eosinophiles	1	1		2
Lymphocytes	12	18	9	20
Monocytes	14	11	20	8
Immature Monocytes	46	47	49	46

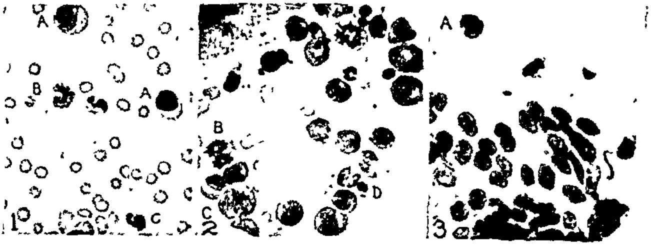

FIG. 2. 1, Peripheral blood: Immature *monocyte*, *A*; mature monocyte, *B*; polymorphonuclear, *C*. 2, Sternal marrow: Portion of megakaryocyte, *A*; monocytoid cell in *mitosis*, *B*; *immature monocyte*, *C*; normoblast, *D*. 3, Smear of fragment of prostate (Wright's stain): Immature monocyte, *A*.

There existed anemia, thrombocytopenia and leucocytosis with about 50 per cent of the white cells being of the atypical immature variety of monocytes (fig. 2, *1*). Sternal marrow was aspirated by the aid of a short 20 gauge styletted needle. Figure 2, *2* illustrates the type of cell seen in the marrow, which was decidedly hyperplastic. Many of the immature monocytoid cells were in mitosis. (Two can be observed in figure 2, *2*.) Approximately 75 per cent of all of the bone marrow cells were immature monocytes. They appeared to grow in sheets. Figure 2, *3* is a photomicrograph of a smear of a fragment of prostate removed by transurethral electro-resection. These fragments were exposed to distilled water as they were cut and so their staining characteristics have been distorted. However, the average hematologist could easily recognize that the majority of the cells were atypical of immature monocytes. They are more easily recognized in such smears (figure 2, *3*) than in histologic sections (figure 1).

SUMMARY

Another case of monocytic leukemia is presented; the second known case in which the presenting symptoms were those of prostatic urinary obstruction. The repeated episodes of complete urinary retention can be explained on the basis of recurrent exacerbations of edema of the prostate secondary to the leukemic infiltration. Alleviation of the obstructive symptoms by cystostomy, if transureteral electro-resection is impractical, is indicated in such cases.

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HEMATURIA IN WORKMEN IN ANILINE DYE INDUSTRY DUE TO 5 CHLORO ORTHO TOLUIDINE SIX CASE REPORTS[1]

JAMES S LYONS

The aniline dye industry, of recent years, has greatly expanded in America and medical interest in physical conditions occurring in workmen in this industry, as a result of the handling of chemicals, has correspondingly increased.

During the past 25 years I have had occasion to examine a number of aniline dye workers For the most part, these men presented symptoms of increased urinary frequency or hematuria and were examined for possible malignant disease of the bladder In association with these conditions, a history of long continued contact with the causative chemical agent was usually obtained

In May 1941 I first encountered a new condition presented by workmen in this industry This condition was characterized by hematuria and resulted from a single contact with a specific chemical Such an occurrence was in direct contrast with my experience and a review of the American literature failed to disclose any reference to this acute type of poisoning The only article referring to this type of poisoning emanated from England Also, upon investigation, I found that these cases were not isolated happenings but resulted from the handling of this chemical in a definite process used in manufacture

Therefore, I believed it advisible to report this series of cases illustrative of immediate damage to the urinary bladder dependent on a single contact with a specific chemical

The particular chemical is 5 chloro ortho toluidine This substance may be regarded as a derivative of ortho toluidine or para chloraniline Due to differences in foreign and American terminology and to avoid possible confusion as to the substance under consideration, it may also be designated as 2 amido 5 chlor-toluol

At the dye plant the chemical is received as a hydrochloride salt For commercial use, this salt must be put through certain processes The first process, in use in 1941, consisted of grinding, mixing and diluting The end product was the unchanged dry hydrochloride salt In the present process, the hydrochloride salt is received as a wet paste This is converted into a diazo salt and in this process the 5 chloro ortho toluidine loses its identity

Commercially 5 chloro ortho toluidine, in the form of its hydrochloride salt, is used as an intermediate for azo dye stuffs Yarns or woven cotton goods are impregnated with this chemical The chemical of itself is a white powder and with the addition of other chemicals, colors are produced The formation of the color takes place by reaction within the fiber of the material A fast color is thus produced

In carrying out these processes, workmen come in contact with the chemical The danger of poisoning is recognized in the industry and workmen are provided protection by the use of respirators, coverall clothing and gloves. Two portals of entry into the body are possible, by inhalation or absorption through the skin. However, by accident or carelessness instances of poisoning do occur.

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[1] Read at annual meeting, Western New York and Ontario Urological Society, Central Section of the American Urological Association, Alexandria Bay, N Y, September 14, 1946

My first experience with poisoning by this chemical occurred on May 20, 1941. Two workmen were admitted on my service at St. Peter's Hospital. Both had been employed in handling 5 chloro-ortho-toluidine and had become ill at the same time. I will give these two cases in detail as they present the typical picture of poisoning by this chemical.

CASE REPORTS

Case 1. E. G., a man aged 25, the day previously had been employed shoveling the dry chemical into barrels. In the afternoon he noticed that his finger nails had turned slightly blue in color. Later he had severe pain on voiding and that evening passed blood in the urine. He had to void frequently during the night and each time the urine was bloody. The following morning he had to void every few minutes and blood was still present in the urine. The patient was questioned as to manner of contact with the chemical. He stated that at times the respirator became uncomfortable and he removed or lifted it away from his face. Also, that as a barrel filled, he grasped the edges of the barrel and shook or rocked it. He was wearing heavy canvas gloves but felt that the chemical dust worked through his gloves or that dust came in contact with his hands, when gloves were removed.

General physical examination was negative except for marked tenderness just above the pubis.

Laboratory findings: red blood cells 5,240,000; white blood cells 9,000; hemoglobin 85 per cent; polymorphonuclears 80 per cent; lymphocytes 18 per cent: eosinophiles 2 per cent. Blood chemistry: nonprotein nitrogen 36 mg., urea 18 mg. The Wassermann test was negative. The urine was grossly bloody, reaction was acid. Microscopically the urine showed many red blood cells and masses of epithelial cells. Stained smears of urinary sediment were examined but no organisms were found. Urine cultures were sterile.

Case 2. D. C., a man aged 26, the previous day had been employed filling barrels with the dry chemical. During the afternoon he had severe pain on voiding and later he noticed a blue color of lips and finger nails. That evening he had marked frequency in urination and the urine looked dark in color. Throughout the night he had continued frequency in urination and urine became bloody. In the morning he had to void every 10 minutes and noticed that urine was red and that pain on voiding was severe. This man was working with patient reported as case 1 and working conditions were the same.

No abnormalities were found on physical examination and the only positive finding was marked tenderness just above pubis.

Laboratory findings: Red blood cells 4,840,000; white blood cells 8,400; hemoglobin 86 per cent; polymorphonuclears 65 per cent; lymphocytes 34 per cent; eosinophiles 1 per cent. Blood chemistry: nonprotein nitrogen 35 mg., urea 16 mg. The Wassermann test was negative. The urine was grossly bloody, specific gravity 1020 and reaction was acid Microscopically there were many red blood cells and masses of epithelial cells No organisms were found in stained smears of urinary sediment and urine cultures were sterile

DISCUSSION

These 2 cases may be considered jointly, as they followed the same clinical course Temperature, pulse and respiration remained normal throughout In case 2 there was one vomiting attack on the second day but otherwise nausea and vomiting did not occur During the first 2 days there was moderate abdominal distention, which was relieved by enemas The first 3 days the patients were kept on a liquid diet Twenty four hour fluid intake averaged between 3000 and 4000 cc The urinary output averaged between 1,500 and 3000 cc Blood counts were taken daily and blood nonprotein nitrogen and urea were checked daily At no time during the course of illness did blood changes or evidence of renal insufficiency become manifest Pain on voiding was intense for the first 2 days Morphine gr $\frac{1}{8}$ was given as necessary The urine was grossly bloody for 3 days On the fourth day the urine had cleared but microscopically showed red blood cells, 25 to 50 per high power field Urinary frequency was reduced to hourly intervals After 5 days the condition had greatly improved and cystoscopic examination seemed feasible

On cystoscopy the bladder presented a most remarkable picture So typical were the changes in the bladder, due to the action of 5 chloro ortho-toluidine, that a description of the cystoscopic appearance of the bladder, observed in these first 2 cases, would be identical with the picture presented by all subsequent cases examined

The entire bladder was involved and appeared as though the mucosa had been brushed over with an electrocoagulating current, with subsequent inflammatory reaction The mucosa was raised in thickened, rigid folds, that were roughly parallel to each other and extended backward from the vesical orifice The folds could not be flattened out by filling the bladder The surface of the mucosa was grayish in color and had the appearance of a sloughing or exfoliating membrane Underlying this grayish membrane and in the depths of the folds the mucosa was dark purplish red in color and there were numerous hemorrhagic ulcerations The trigone and ureteral orifices could not be distinguished

X-ray of the urinary tract showed the kidneys to be normal in size and position There were no calculi Diodrast, 20 cc was injected intravenously There was prompt excretion and good concentration of Diodrast by either kidney Calyces, renal pelves and ureters appeared normal

The clinical course, from this point, was uneventful and both patients were discharged on fifteenth hospital day, with complete relief of symptoms Urinalysis on discharge showed 10 to 20 red blood cells per high power field The patients were kept under observation and by the twenty-second day following onset of symptoms, blood cells had disappeared from the urine

Cystoscopy was repeated at this time In case 1 the bladder appeared normal In case 2, the bladder appeared normal except for small hemorrhagic appearing areas just lateral to either ureteral orifice. Complete urologic investigation was carried out and in each case kidneys, ureters and bladder were found to be normal. At the end of 3 months, cystoscopic examination was repeated. In both instances a normal urinary tract was demonstrated and the possibility of remote effects from this type of poisoning, was eliminated.

The next 4 cases of poisoning by this chemical occurred as follows: Two in May 1942; 1 in June 1943 and 1 in October 1944. These workmen were engaged in handling the wet hydrochloride paste in a new process.

They were required to wear complete protective clothing including rubber gloves but nevertheless contact with the chemical did occur. In each case a history was obtained of a small amount of the chemical coming in contact with the skin of forearms or hands. In 2 cases, only 2 or 3 drops of the chemical splashed onto the skin of the forearm.

In each instance dysuria developed within a few hours and blood appeared in the urine within 4 to 12 hours. Intense pain on urination was the chief complaint. In these 4 cases the urine was grossly bloody for an average of 5 days. Each case pursued the same clinical course as detailed in cases 1 and 2. At no time was there any evidence of blood changes or renal insufficiency.

Following subsidence of acute symptoms on fifth or sixth day cystoscopic examination was done. The bladder in all cases showed the same exfoliation of the mucosa with intense inflammatory reaction, as previously described. Intravenous urography demonstrated good renal function and normal calyces, pelves and ureters. In these 4 cases blood cells had disappeared from the urine by the end of the third week. At this time cystoscopic examination showed restoration of the bladder mucosa to normal. Patients continued in good condition and re-examination 3 months following the acute poisoning, demonstrated, in each instance, a normal urinary tract.

Following this experience a search of the literature was made. As previously stated no report of this condition was found in the American literature. The only article found was by Currie of England. In this article, published in 1933, 11 cases of hematuria, following contact with 5 chloro-ortho-toluidine, are reported. The subject is considered entirely from the industrial standpoint. No urologic investigation was done but from the masses of bladder epithelium present in the urine, Currie assumes that the bladder is chiefly involved in this type of poisoning. Currie states that their first experience with cases of this type occurred in 1930. At this time the poisonous nature of the chemical was unknown. Inquiry through the International Labour Office, Geneva, elicited the fact that some trouble had been experienced in continental factories in handling this substance. Further reports of continental experience are unobtainable at present.

SUMMARY

5-chloro-ortho-toluidine is a toxic substance that readily enters the body by inhalation or skin absorption. It is of interest to note that 4- and 6-chloro-ortho-toluidine have been handled in considerable quantities in the aniline dye industry, without toxic effect.

In this series of cases skin absorption appeared to be the important avenue of entrance into the body.

The specific toxic action is on the urinary bladder. Symptoms of bladder involvement appear within a few hours following absorption of the chemical. Acute poisoning is evidenced by severe pain on urination, marked frequency in urination and hematuria. Cystoscopy reveals an acute hemorrhagic cystitis with exfoliation of the superficial layers of the mucosa.

Recovery is complete within 3 weeks. Urologic examination at end of 3 months showed a normal urinary tract and proved that there are no remote effects from this type of poisoning.

5-chloro-ortho-toluidine poisoning presents an instance of immediate damage to the urinary bladder dependent on a single contact with the chemical.

Six cases of poisoning by 5 chloro-ortho-toluidine are reported, with description of the clinical course and cystoscopic findings.

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GLANDULAR METAPLASTIC MALIGNANCY IN THE URINARY TRACT

REPORT OF 4 CASES

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Tumors in the urinary tract which contain glandular elements are not commonly seen but when they do occur, they present certain practical and theoretical problems: 1) whether the glandular elements represent metaplasia of transitional epithelium to glandular epithelium, 2) whether the lesion is primary in the urinary tract or metastatic from the intestine or other glandular organs and 3) finally, whether the tumor arises from known glandular elements at the attachment of the urachus or around the vesical neck.

Transformation of the urinary epithelium from transitional to glandular type is known to occur in exstrophy of the bladder and is said to take place in cystitis cystica. Metaplasia of this type in tumors was described by Stoerck as early as 1899, and in 1907, Stoerck and Zuckerkandl called attention to the similarity between the glandular tissue of tumors of the bladder and the mucosa of the large intestine.

In a recent review of the literature Foot gives an excellent discussion on metaplasia of urinary tract epithelium and reports 3 cases; the metaplasia occurred in the epithelium of the renal pelvis in 1 case and in the epithelium of the bladder in the other 2 cases. In one of the latter cases a malignant tumor was found (adenocarcinoma). The latest report of a case of this type is by Ackerman. His case was a 66 year old man with a history of renal calculi for about 14 years treated by nephrectomy. The kidney proved to have a glandular type metaplasia of the pelvic epithelium from which developed a mucinous carcinoma at the site of nephrectomy 6 years later. It is interesting to note that of these cases of renal epithelial metaplasia 2 followed calculus disease; this suggests that chronic irritation or other alterations in the environment of cells of the epithelium of the urinary tract may contribute to the development of secretory epithelium.

Emmett and McDonald recorded the clinical and pathologic findings in 9 cases of benign proliferation of glands of the urinary bladder. They differentiated them into the subtrigonal type and into those which they chose to call intestinal type glands. Five of the 9 cases were of the latter type.

Patch and Rhea described a case of a 67 year old woman, who at cystoscopic examination was found to have a sessile tumor of the bladder at the upper extremity of its base. Suprapubic exploration revealed a tumor extending through the peritoneum and confluent with a mass in the tip of the appendix. The uterus was involved or adherent to the mass. The tumor in the bladder was fulgurated and the bladder drained with a permanent suprapubic catheter. The pathologic report was "mucus secreting adenocarcinoma of the bladder."

These authors likewise believe that chronic irritation may cause the mucous membrane of the urinary bladder to undergo metaplastic changes. They also discussed the relationship between cystitis glandularis and mucous secreting adenocarcinoma and between leukoplakia and squamous cell carcinoma. Stirling and Ash have similar views of these proliferative changes.

The ability of urinary tract epithelium to adapt itself to foreign or abnormal environment by the formation of glands is best exemplified in the condition of exstrophy of the bladder. Friedman and Ash and others have pointed out that since the rectum and bladder have a common embryologic origin from the cloaca, it is not surprising that the urinary tract contains rests of glandular elements or that it may transform itself into glandular epithelium. Adenocarcinomas of the fundus of the bladder may be derived from the urachus, but a number of the cases of adenocarcinoma of the urinary tract, including those reported by Foot, have occurred in locations at a considerable distance from the attachment of the urachus and other concepts are necessary to explain the development of these glandular elements in many instances. It is apparent that chronic irritation or other alterations of the environment of the epithelial cells and the fact that urinary tract epithelium has an embryologic origin in common with the rectum are significant.

The question of metaplasia of transitional epithelium is interesting from a theoretical point of view, but from a practical standpoint it is somewhat more important in each individual case of glandular carcinoma of the urinary tract to determine if the tumor is truly primary in that location. It is not possible to establish from morphologic structure alone where an adenocarcinoma may originate, and Ewing has pointed out that it is often difficult and at timesi mpossible to determine whether an adenocarcinoma is primary or secondary in the bladder. It seems not unlikely that some of the cases of adenocarcinoma reported in the literature as primary tumors of the urinary tract may in fact be metastatic in this location.

CASE REPORTS

The following cases are concerned with tumors of the urinary tract which were adenocarcinomas or contained glandular elements.

Case 1. R. E. G., a 64 year old white man, complaining of hematuria, difficulty in urination and nocturia of about 1 year's duration, was seen on March 15, 1943. About 8 months previously, he had begun to have intermittent attacks of total hematuria with the passage of clots. He had had a series of prostatic massages and bladder irrigations but no other treatment. For the past few weeks before admission, he had been having mild suprapubic pain and burning on urination. He had not lost any weight and except for the urinary complaints felt fairly well.

Cystoscopic examination on March 28, 1943 revealed a medium sized, meaty, infiltrating tumor in the fundus and on the left lateral wall. On bimanual examination under anesthesia a large mass involving the left lateral wall of the bladder could be easily palpated.

The bladder was still freely movable and the impression was that there was a good chance of completely resecting the growth. Biopsy confirmed the diagnosis of infiltrating carcinoma of the bladder but no unusual features were noted in this specimen.

At operation on April 14, 1943 a large, firm mass was encountered involving the entire left lateral wall of the bladder and densely adherent to the peritoneum but showing no signs of extension beyond the peritoneum. The peritoneum was incised above and below the tumor, and that portion of the peritoneum which was adherent to the tumor was resected and the edges of the peritoneum resutured. The bladder was incised in the midline anteriorly and at a distance of from 1.5 to 2.5 cm. from the tumor in what was felt to be normal bladder wall; the tumor was resected with the high frequency current. A 5 F. ureteral catheter was passed through the left ureter to the kidney and left in place. At the vesical neck, there was a margin of about 2.5 cm. of normal bladder wall. The resection was carried down to within 1.5 cm. of the ureteral orifice on the left side. An unusual feature was noted in the microscopic slides prepared from this surgical specimen in that a portion of the tumor was covered by glands which bore a resemblance to intestinal mucosa.

The patient went home with an indwelling urethral catheter because the suprapubic wound closed slowly. He continued to wear the catheter until the suprapubic wound healed and on examination 4 months after operation rectal palpation revealed no evidence of a recurrent tumor in the base of the bladder. Suprapubic palpation gave no indication of any mass within the abdomen. Bladder capacity was 5 ounces at that time.

When seen 5 months postoperatively the patient felt well and had no urinary symptoms. Nine months postoperatively, he began to complain of dysuria, frequency and urgency. About a month later he began having hematuria and finally the suprapubic wound broke down and he died 1 year postoperatively of recurrence of the tumor.

The neoplasm in this case morphologically resembled the ordinary anaplastic infiltrating carcinoma of the bladder, but there appeared on the lining surface of the tumor a striking conversion of the neoplastic epithelium to the secretory type (fig. 1). Consequently, it seems not unreasonable to assume that the glandular metaplasia developed as a result of some unknown environmental factor to which even neoplastic cells of urinary tract epithelium are able to respond by forming glands. The results of clinical examination, the morbid anatomy of the lesion, and the subsequent course of the patient all indicate that the tumor in this case was primary in the bladder and not metastatic from some other source.

Case 2. A. H., a 48 year old woman, was seen on January 2, 1946 because of difficulty and pain on urination of several weeks' duration. She had had no hematuria and had never passed a stone.

On cystoscopic examination a tumor, 2 cm. in diameter, was found in the right lateral dome of the bladder. A biopsy taken at this time was reported as adenocarcinoma (fig. 2).

At subtotal cystectomy on January 9, the tumor was found to be somewhat larger than anticipated and involved a small area of the parietal peritoneum over the dome of the bladder. This was handled as in the preceding case, care being taken to remove a margin of normal bladder wall for a distance of from 1.5 to 2.5 cm. along with the tumor.

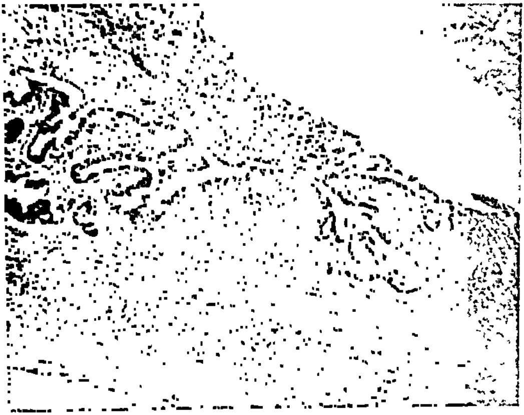

FIG. 1. Case 1. Glands on surface of infiltrating tumor of bladder. (H & E, × 45)

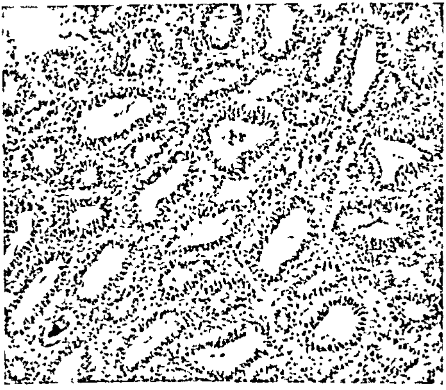

FIG. 2. Case 2. Biopsy specimen of adenocarcinoma. (H & E, × 100)

The pathologic report was adenocarcinoma of the bladder with a note suggesting the possibility of a primary site in the gastro-intestinal tract because of peculiar bowel-like glandular structures included in dissection. Although the operative procedure and the postoperative course of the patient did not indicate that the bowel had been entered, a gastro-intestinal series was done and revealed no abnormality of the gastro-intestinal tract.

Cystoscopy on June 1, 1946, six months after operation, showed no evidence of recurrence of the tumor in the bladder. Bladder capacity at that time was 250 cc. The patient looked and felt well and was having no urinary symptoms. Eight months after operation she returned with recurrence of symptoms referable to the bladder including pelvic pain. She was referred for deep roentgentherapy.

This was a case of adenocarcinoma which was not morphologically distinctive. In the microscopic sections it was not possible to trace the relationship of the tumor cell nests, which extended underneath the mucosa at the edges of the crater, to other structures. From this standpoint it seems possible that the neoplasm may have involved the bladder as a metastatic lesion. However, from a clinical point of view, a careful review of the case failed to reveal any other possible primary focus, either at the time of operation or several months later. In this case the glandular structure of the carcinoma existed throughout the lesion and it is assumed that the tumor arose from a metaplastic plaque of glandular epithelium in the urinary tract.

Case 3. T. H. W., a white physician, 73 years old, was admitted on October 18, 1945 because of hematuria of 5 days' duration. Five years before, the transverse colon had been resected for carcinoma of the intestine. However, since that time, the patient had gained weight and had had no further gastro-intestinal complaints; his appetite was good and the bowel habit regular.

Cystoscopy under spinal anesthesia showed a medium sized tumor on the trigone of the bladder extending up toward and involving the urethrovesical junction. On bimanual examination under anesthesia the mass could be easily outlined.

On November 2, 1945 the tumor and a portion of the prostate were resected transurethrally with a McCarthy resectoscope and 16 nonremovable radon seeds, 0.25 mc. each, were implanted in the base of the tumor. The pathologic report was "adenocarcinoma of the bladder containing gland-like structures resembling those found in the large bowel."

When last seen, 9 months postoperatively, the patient had no urinary symptoms and his general health was good; cystoscopy showed no evidence of tumor in the bladder and a well healed scar at the site of resection. Rectal palpation gave no suggestion of local extension or recurrence of the tumor.

This is an example of adenocarcinoma of the bladder in which there is a strong probability that the primary malignancy existed in the transverse colon and was removed 4½ years before development of the secondary adenocarcinoma in the bladder. The morphologic picture of the neoplasm is consistent with this view. The unusually prolonged interval between resection of the colon and the development of symptoms referable to the bladder and the fact that signs or symptoms of metastasis to other organs did not develop before or after the urologic procedure tempt speculation on the possibility that the tumor of the bladder may be primary rather than metastatic from the colon. However, the evidence is stronger in favor of the colon as the primary site of the neoplasm. The case is introduced to illustrate how difficult it is to determine whether an adenocarcinoma in the urinary tract is primary or secondary in that location, even if carcinoma is known to have existed in another glandular organ.

Case 4. T. M., a 41 year old white man, was admitted on July 20, 1946 because of pain in the right thigh extending from the groin to the knee of several months' duration. The pain became worse when urinating. For several months he had been having pain in the lumbosacral region on the right side whenever he stood up for a long time.

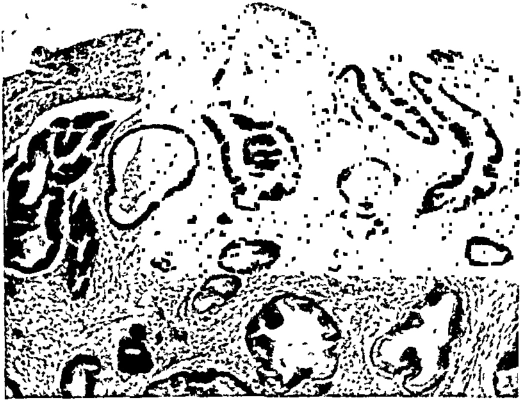

FIG. 3. Case 4. Glands which communicate with the lumen of the ureter (adenocarcinoma). (H & E, X 100).

The patient gave a history of an intermittent, mild cough since the age of 15 years. In July 1945 a roentgenogram revealed a mass in the left lung. The cough had persisted and when first seen was productive and at times blood tinged. He had lost 25 pounds since July 1945.

A roentgenogram of the chest on July 21, 1946 showed large areas of increased density in the left lower lobe, scattered, infiltrated lesions throughout both lungs and multiple small abscesses. Excretory urograms indicated a normally functioning left kidney but a nonfunctioning right kidney. An outline of the right kidney suggested no alteration in the size or shape.

The right ureter was catheterized with a No. 6 catheter and during cystoscopy an impassable obstruction was met at about the midportion. A right ureterogram showed complete obstruction at the midportion of the ureter. A diagnosis of possible tumor of the renal pelvis with extension down the ureter or primary ureteral tumor was then made.

The right kidney and part of the ureter were removed on August 7, 1946.

The pathologic report rendered by Dr. F. H. Colvin, Jr. was "adenocarcinoma of the ureter, Grade I, invading the perineural and perivascular lymphatics of the ureter. Gross retention cysts of the kidney, hydronephrosis and severe pyelonephritis." Dr. Colvin expressed the opinion, "The contention that the tumor is primary in the ureter is supported by the fact that certain of the glandular formations open directly into the lumen of the ureter" (fig. 3).

Sections of the tumor were submitted to the American Registry of Pathology and in a personal communication to Dr. Colvin, Col. J. E. Ash, agreeing with Dr. Colvin's opinion that the tumor was probably primary in the ureter, wrote: "There are a number of instances in which enteric derivatives have been found higher than the bladder. Most of these are mucinous adenocarcinomas of the renal pelvis. We have one spectacular case in which pelvic plaques of unequivocal gastroduodenal glands of the pyloric or Brunner type were present."

In this case the adenocarcinoma apparently arose from the epithelial lining of the ureter because the tumor was located on the lining surface of the ureter and the tumor cell nests diminished in number in the direction of infiltration towards the periphery. Here again the question of whether the tumor is primary or secondary in the urinary tract is complicated by the presence of possibly malignant lesions in the lungs and evident involvement of the lumbar plexus of nerves by carcinoma.

SUMMARY

Four cases of glandular carcinoma of the urinary tract, illustrating the difficulty of determining whether an adenocarcinoma is primary or secondary in this location, have been reported. In 1 case the tumor of the bladder was probably metastatic from a carcinoma of the colon. In 2 cases the adenocarcinoma probably arose from plaques of urinary tract epithelium which had undergone metaplasia to the secretory type. In 1 case metaplasia of the epithelium to the secretory type evidently occurred in an infiltrating transitional cell carcinoma.

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IMPOTENCE FOLLOWING TRAUMA TO CORPORA CAVERNOSA RELIEVED BY CARTILAGE GRAFTS: A CASE REPORT

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Injuries involving the external genitalia were encountered not at all infrequently among battle casualties at O'Reilly General Hospital. Although such injuries were relatively uncommon as compared to other parts of the anatomy, a number of them presented extremely difficult and unusual surgical problems calling for originality in operative treatment. The following case is presented because a method which we have not seen described previously was employed in correcting impotentia resulting from traumatic destruction of the corpora cavernosa.

In our search of the literature, the *Journal of the American Medical Association's* Moscow correspondent mentioned in the August 24, 1946 issue that I. Goldin "described transplantation of cartilage as the operation of choice for straightening a traumatically bent penis." Since this item suggests that the Russians preceded us in the development of the operation which we are presenting, we offer apologies if more specific acknowledgement is due. Regardless of who receives credit for originating the operation, we believe that the following case is sufficiently unusual to afford interest to anyone concerned with trauma of the genitalia.

CASE REPORT

Hospital Register Number 38946, a 26 year old white soldier was admitted to O'Reilly General Hospital on March 3, 1946. He had been wounded in action in the South Pacific on July 16, 1944 by an exploding "booby trap." At that time he suffered a compound comminuted intratrochanteric fracture of the left femur, compound fracture of the right ulna, a lacerated wound of the scrotum with traumatic avulsion of the left testicle, and an extensive lacerated wound of the penis involving both corpora cavernosa. On the same date the record states that "the scrotum was repaired by apposition of flaps preceded by thorough examination of left testicle which was left in situ. The corpora cavernosa were loosely sutured into position. A dorsal slit of foreskin was done. A catheter was inserted through the urethra into the bladder and clear urine was obtained. The wound of the left thigh was débrided and packed with vaseline gauze." Prior to admission to O'Reilly General Hospital the patient underwent prolonged treatment at several General Hospitals for non-union of the right ulna, paralysis of the right median nerve, paralysis of the left peroneal nerve and osteomyelitis of the left femur. The scrotal and penile wounds healed promptly and no further attention was given them in view of the more urgent nature of the other injuries. When treatment was completed, he was transferred to O'Reilly General Hospital, a plastic surgery center, for possible repair of the defects of the penis and scrotum.

On admission, examination showed a rather extensive depressed defect in the left groin just below the medial attachment of the inguinal ligament. This defect consisted of dense scar tissue which was attached by tight, short fibrous bands to the lateral aspect of the shaft of the penis to a point 1 inch proximal to the corona. These fibrous bands caused marked left lateral deviation of the penis, keeping it almost immobile in close proximity to the left thigh (fig. 1). The left testicle had apparently atrophied completely for it could not be palpated anywhere in the scrotal or inguinal regions. The right testicle was normal. On examination of the penis, the glans was apparently intact. The prepuce was somewhat redundant ventrally. The left corpus cavernosum was represented by longitudinal bands of fibrous tissue except at the base of the penis where the left crus appeared to be intact. On the right side, a depressed scar was present in the midportion of the penile shaft and the corpus cavernosum was apparently completely destroyed. The patient noted that on erection there was some distention of the glans and a definite erection of about ½ inch at the left side of the base of the penis. The main portion of the penile shaft was completely flaccid during erection. Sensation was intact over the entire penis and libido was normal. Coitus was impossible not only because of the marked lateral deviation of the penis but also because of the flaccid penile shaft.

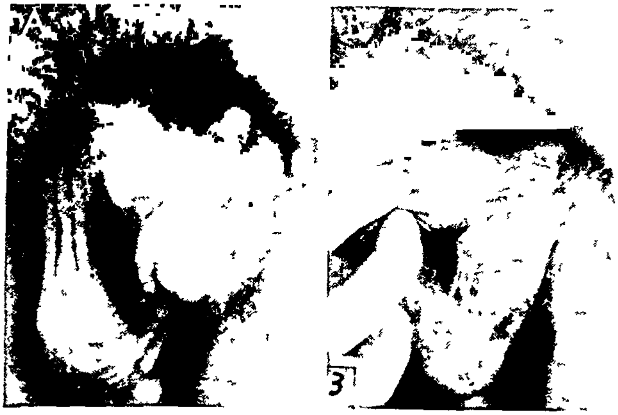

FIG. 1. Preoperative photographs. *A*, Anterior view, showing marked deviation of penis to left by scar tissue adhesions to inner thigh and inguinal region and loss of substance in flaccid shaft of penis. *B*, Anterior view, demonstrating bands of dense scar tissue causing lateral deviation of penis.

The patient was extremely worried about his impotence. He was depressed for long periods of time and took very little part in ward or hospital social activities. He voluntarily stated that he would submit to any treatment which offered the slightest hope of improvement. Our first efforts were aimed at correcting the lateral deviation of the penis. This was accomplished by removing the fibrous adhesions between the shaft of the penis and the groin, and covering the resulting defect in the shaft of the penis with scrotal tissue. On April 18, 1946, under spinal anesthesia, all scar tissue was excised from the left side of the shaft of the penis and the left groin. The defect on the penis and part of the groin was covered by advancement of scrotal tissue, and the remaining defect in the groin was covered by a rotation flap from the medial surface of the left thigh. The postoperative course was uneventful and after healing was complete the lateral fixation of the penis was entirely eliminated (fig. 2). On June 17, 1946 a cartilage graft was inserted to replace the fibrotic left corpus cavernosum. Under general anesthesia, Major Bert Jeremiah removed two costal cartilages, one of which had a small piece of rib attached, while the writers performed the plastic penile operation; one costal cartilage was left under the skin of the chest incision for future use. On attempting to catheterize the bladder, a filiform stricture was encountered in the midportion of the pendulous urethra. Dilatation to 24 F. was easily accomplished and a No. 20 soft rubber catheter left in situ as a guide during the operation.

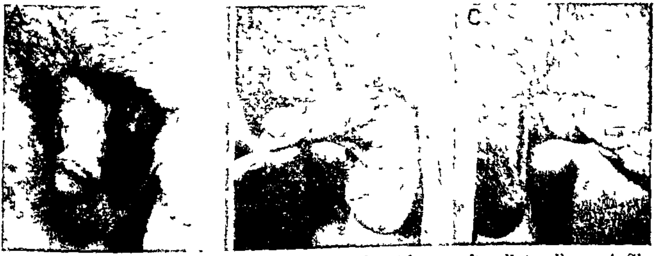

FIG. 2. After penoscrotal plastic and insertion of cartilage graft unilaterally. *A*, Showing result of penoscrotal plastic procedure and appearance of penis following insertion of cartilage graft replacing destroyed left corpus cavernosum. *B*, Left lateral view, showing correction of lateral deviation and flaccidity of shaft of penis. *C*, Right lateral view showing defect in right corpus cavernosum prior to second cartilage graft operation.

An incision was made extending throughout the length of the left side of the penis and carried through Buck's fascia, which was found to be intact. The fascia was undermined in all directions to form a fossa into which a piece of cartilage measuring 2½ inches in length, ½ inch in width and ⅜ inch in thickness could be easily inserted. The proximal ½ inch of the graft consisted of bone. The implant was fixed in position by a single deep suture of No. 30 cotton at each end; the anterior suture was taken through the fascia overlying the posterior surface of the glans; the posterior suture was carried well into the distal end of the intact portion of the left corpus cavernosum. Buck's fascia was then closed over the cartilage implant with interrupted sutures of No. 30 cotton. The skin was closed with C black silk interrupted sutures.

A prophylactic course of penicillin was given for a period of 10 days after operation. A rise in temperature to 102 degrees was noted for 2 days postoperatively and was attributed to the urethral dilatation, since neither chest nor penile wound appeared to be infected. The postoperative course was otherwise uneventful and healing was complete after 10 days. The implant remained in its fixed position and gave rigidity to the shaft of the penis, making it possible to guide the penis by grasping it between thumb and forefinger at the base. On erection, the graft remained impinged upon the functional erectile tissue at the base and upon the glans anteriorly, giving continuity to the organ as a whole and the ability to push against moderate resistance without collapsing.

Three weeks after operation coitus was successfully accomplished by the patient and his comment indicated that the result was completely satisfactory to him but that if more "substance" could be given the penis without jeopardizing the eminently satisfactory result thus far obtained, he would request that we carry out the original plan to place a similar implant on the right side of his penis. Since the circumference of the erected penis was little greater than the implanted cartilage, we decided on a second implant to increase the penile mass, feeling that it would in addition act as further support against possible trauma during coitus without endangering the success of the previous operation. The change in the patient's emotional status was indeed remarkable. He no longer showed any signs of depression; in fact, he told his fellow patients about his injury and operation for the first time, and even seemed to enjoy the inevitable joking which followed. He began to take part in all the social events on the ward and his requests for passes rose to a normal level.

On July 15, 1946 a similar plastic procedure was performed on the right side of the penis. The urethral stricture had remained dilated; a 24 F. guiding catheter was easily passed. It was necessary to excise the scarred skin and subcutaneous tissue. A scarred defect in Buck's fascia was also excised following which it was possible to undermine the fascia and proceed as in the previous operation. The only variations in the procedure were the insertion of two continuous No. 36 removable stainless steel tension sutures to support the suture line in Buck's fascia, in the manner recommended by Cordonnier for repair of urethrocutaneous fistulas, and the use of a piece of cartilage which had not been removed with bone attached. The postoperative course was completely uneventful. Prophylactic penicillin was again given. The skin sutures were removed in 8 days and the steel stay sutures in 10 days. Healing was prompt and complete at that time. The second cartilage graft did not maintain itself in as good position as the first. The anterior end worked itself slightly medially and dorsally. However, it accomplished its prime purposes in adding substance to the penile shaft and support to the first cartilage graft. Three weeks after surgery, the patient again began to have relations and he noticed a marked increase in his sexual efficiency. At no time did he complain of any pain or discomfort on coitus due to the rigidity of the implanted material, a complication which we had feared from the beginning.

Examination of the penis at this time showed some improvement in its general appearance, although the defect in the right lateral surface had not been completely eliminated. The penis was short but of ample circumference. On palpation, the left cartilage implant was in a perfect position of replacement for the corpus cavernosum; the right cartilage was slightly postero-lateral in position (fig. 3). On erection, the penis was elevated to a horizontal position, a surprising phenomenon which we attributed to possible support from slight function in the corpus spongiosum and close adherence between the bone tissue of the first graft and the functional left crus. Slight deviation to the left was noted on erection, but this, we felt, was due not to adhesion or scar, but to the absent scrotal contents and the depressed defect in the left thigh, for the penis could be straightened manually without resistance.

The prepuce was still somewhat redundant ventrally and laterally; circumcision was not deemed advisable because it was felt that the extra tissue might serve as a protective cushion against trauma to the anterior ends of the grafts.

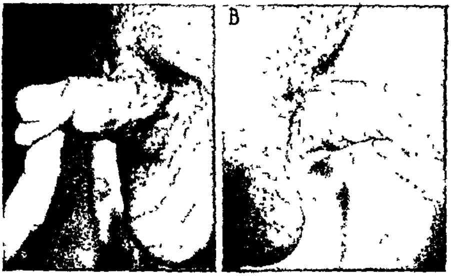

FIG. 3. After second cartilage graft. *A*, Left lateral view, showing rigidity of penile shaft. Scrotal tissue advanced to site of former scar on penis is clearly demonstrated. *B*, Right lateral view, showing improvement in deformity of penis. Redundant prepuce which was left in situ is demonstrated.

COMMENT

As a result of the deformity and functional impairment of the genitalia we were confronted, in this case, with a fairly serious psychosexual problem, which, in our opinion, amply justified an experimental procedure, since it involved no great risk if care was taken to preserve the blood and nerve supply of the penis. In choosing the material to use for the grafts, cartilage was considered to be superior to other foreign materials for the following reasons: 1) It would produce less foreign body reaction. 2) It would maintain its position better because it becomes enmeshed in fibrous tissue which is laid down about it. 3) It could easily be whittled into any desired size or shape at the operating table. 4) It would remain unchanged and resist absorption if postoperative infection did not occur. 5) It would be easy to obtain.

The cartilage with bone attached to the proximal end was chosen because it was hoped that the bone would pick up blood supply from the tissues and maintain its position more securely. This may explain why the first graft remained more secure postoperatively.

The end result exceeded our expectations since all we had hoped for was to make coitus possible by artificially splinting the penis, and we thought it quite unlikely that the patient's sexual life could be restored so near to normal. Although the follow-up period has been brief, there is no reason to expect the repair to break down if the patient heeds the repeated warnings to avoid sexual excesses.

SUMMARY AND CONCLUSION

A case is presented in which cartilage implants were inserted into the penis for impotentia resulting from trauma to the corpora cavernosa.

The successful end result indicates that this simple procedure is practical in restoring sexual function in such cases, which admittedly are very rare.

The theoretical advantages of cartilage over other foreign materials, in the procedure described, are stated.

It is suggested that a small segment of attached rib at the base of the cartilage may be of value in keeping the graft in position.

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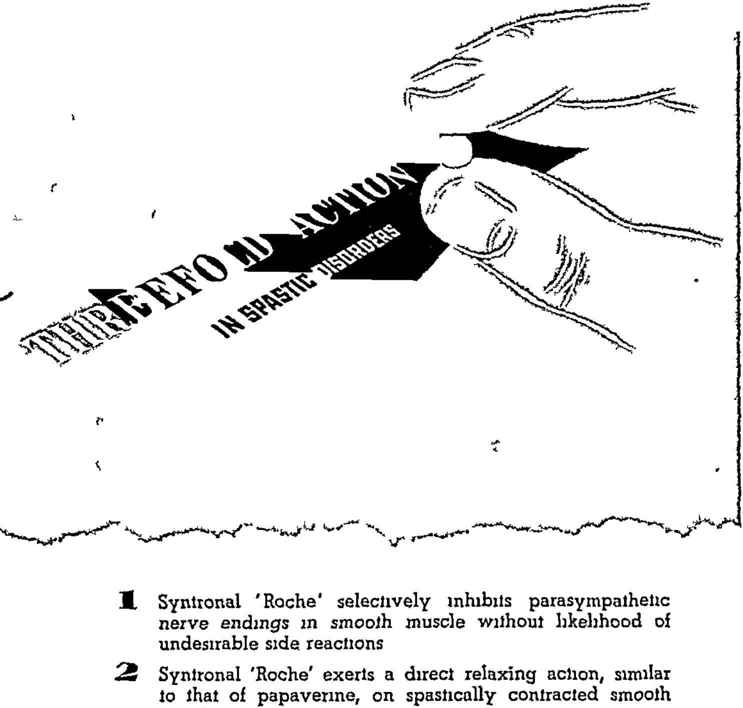

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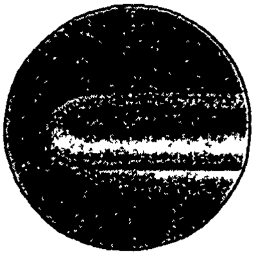

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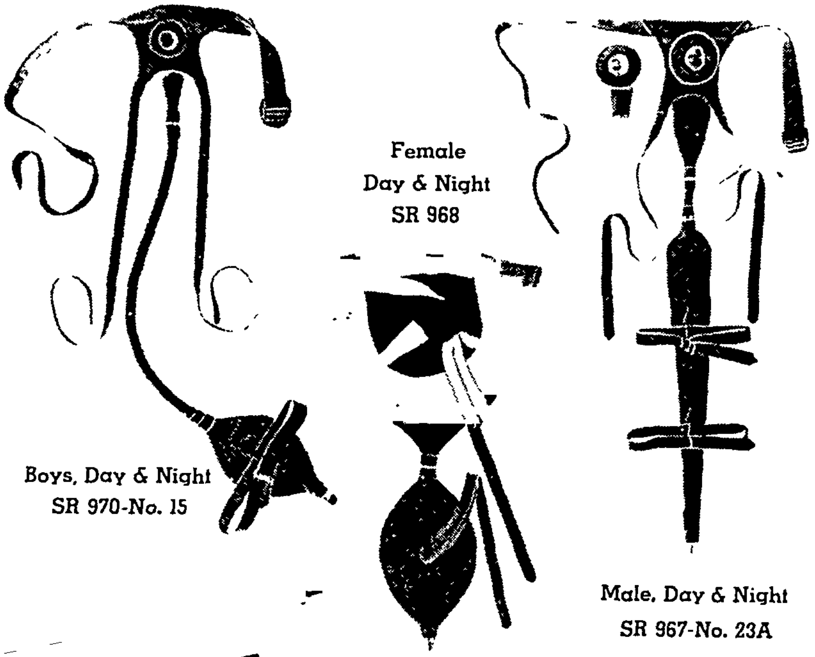

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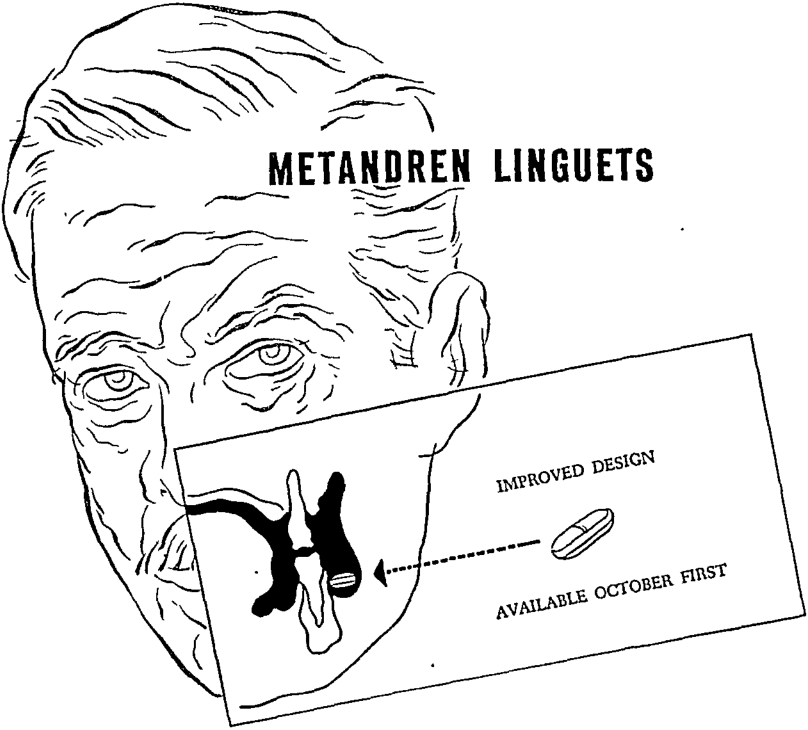

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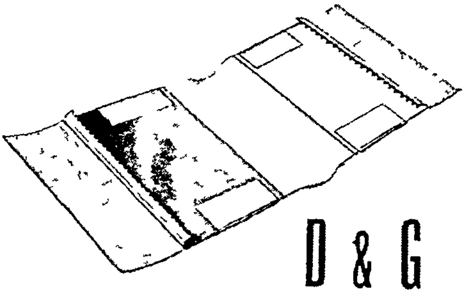

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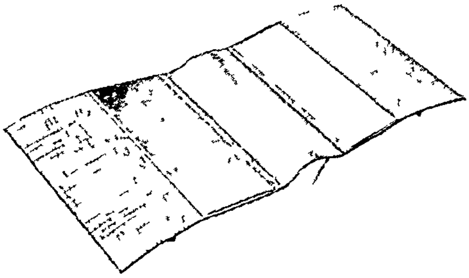

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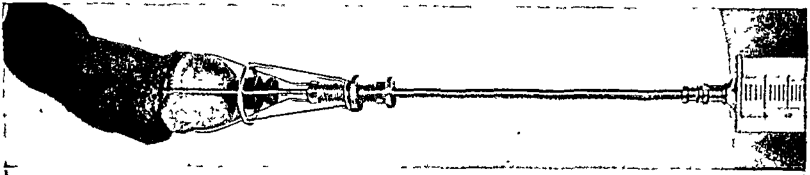

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Ref: "A New Instrument for Urethrography in the Male" M. Leopold Brodny, M.D., Boston. Journal of Urology, Vol. 46, No. 2, August 1941; "Enuresis—The Use of Cysto-Urethrography in Diagnosis" M. Leopold Brodny, M.D., and Samuel A. Robbins, M.D., Boston, Journal of the A.M.A., December 16, 1944.

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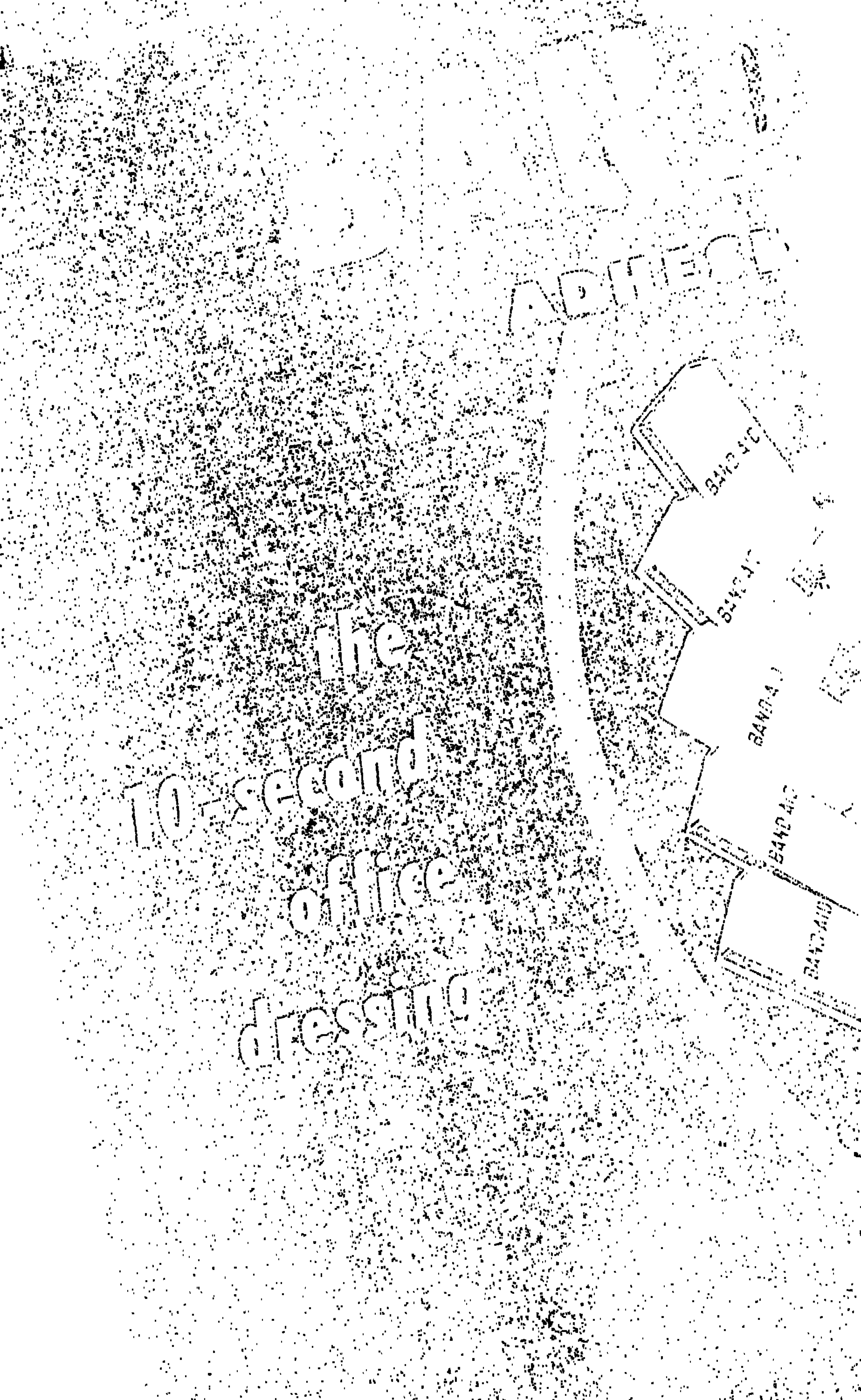
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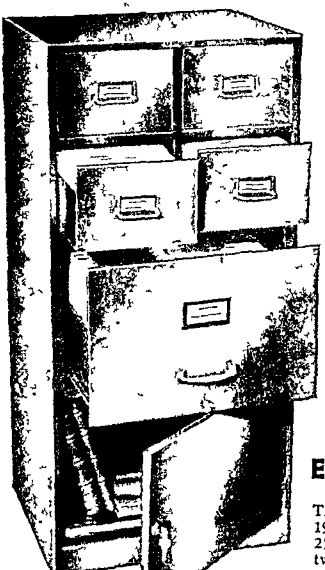

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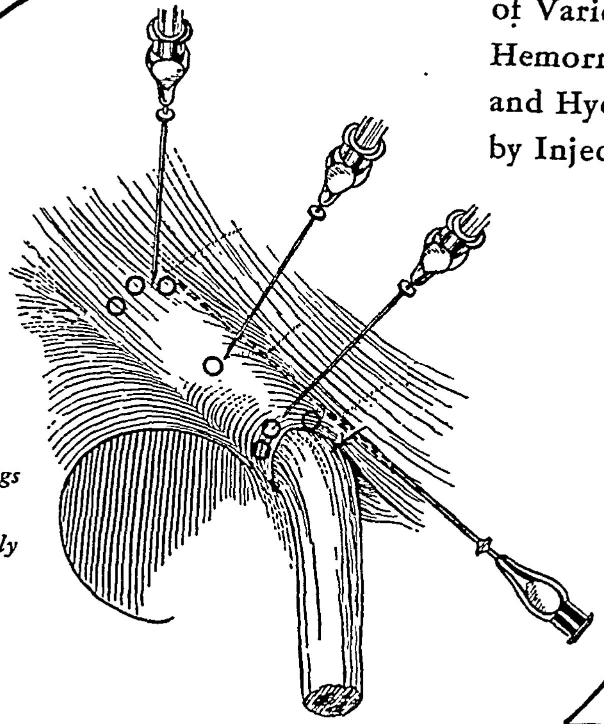

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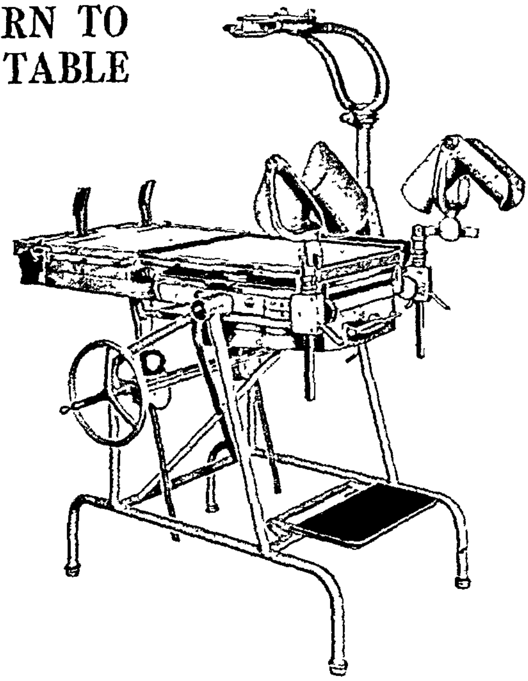

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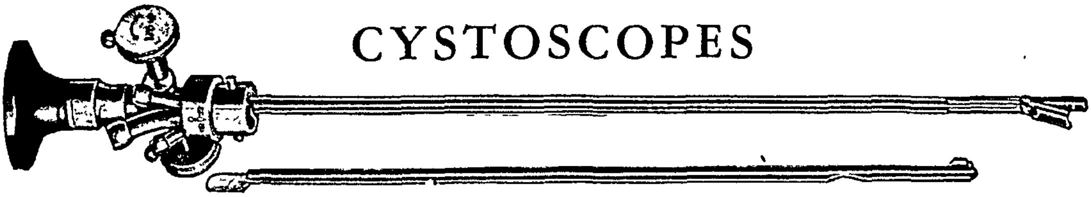

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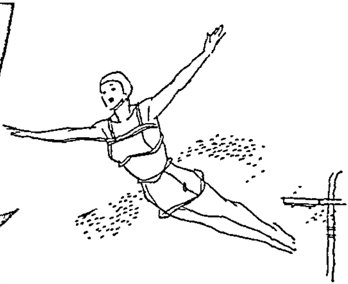

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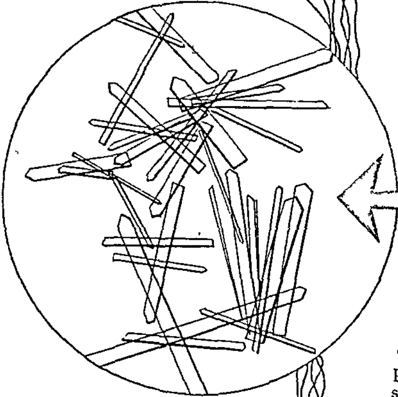

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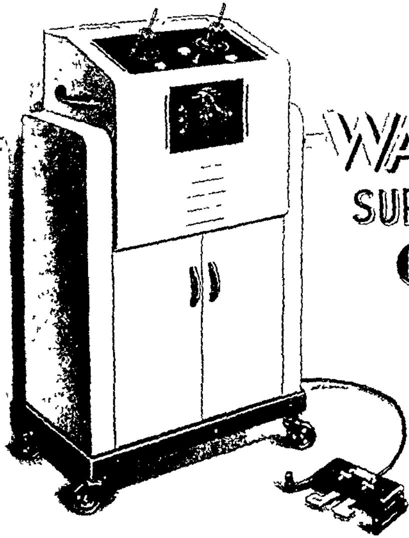

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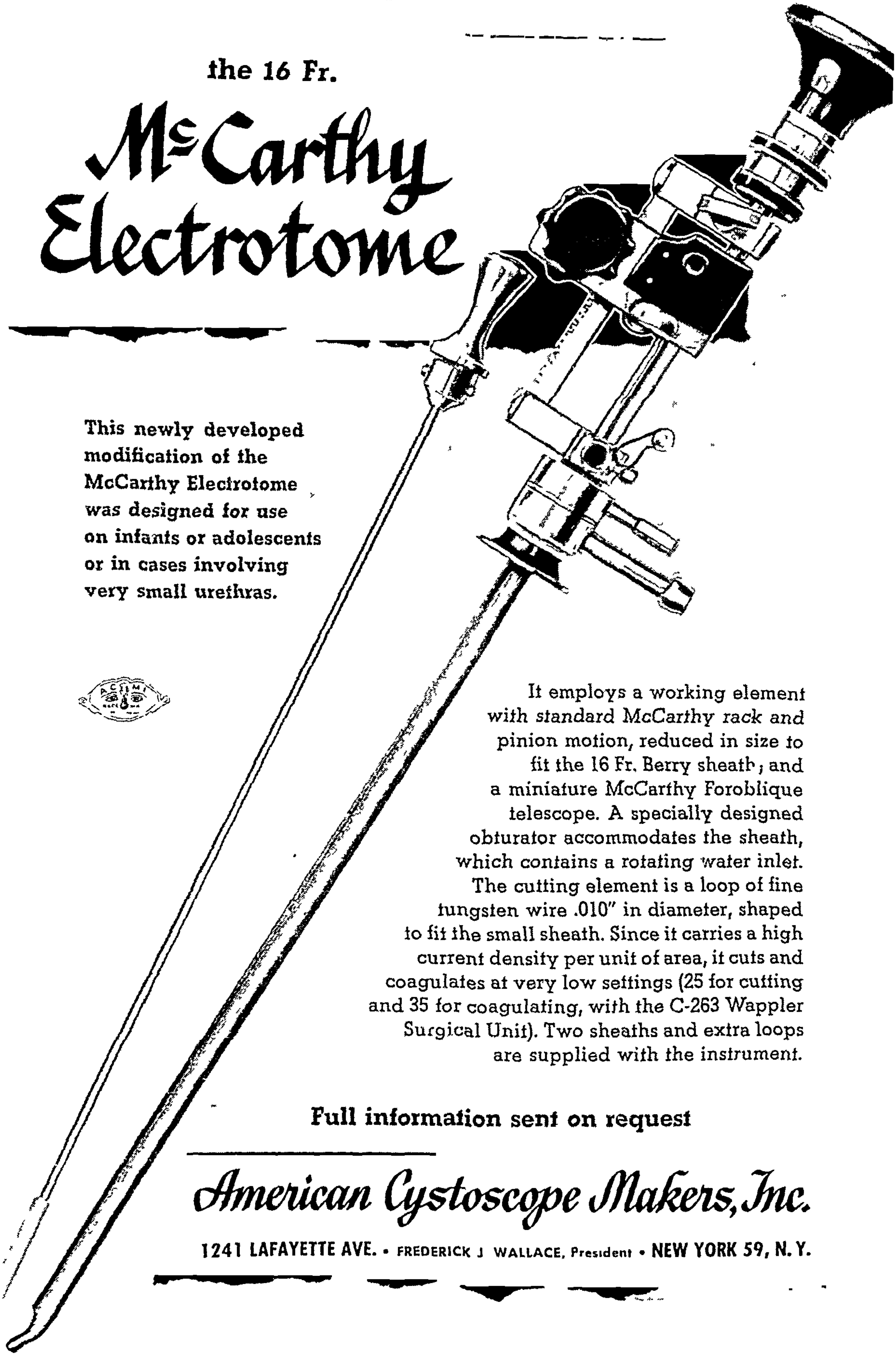

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NONHORMONAL ADRENAL CORTICAL CARCINOMA: REPORT OF CASE WITH 5 YEAR SURVIVAL AND RELIEF OF HYPERTENSION

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A survey of the recent literature on tumors of the adrenal cortex reveals a decided emphasis on hormone-producing neoplasms. This can be readily understood for the following reasons: 1) the striking changes that these tumors evoke in the external configuration of the human body; and 2) the equally dramatic changes that take place following their successful extirpation. On the other hand, the paucity of reports of nonhormone-producing tumors can be ascribed to: 1) their rarity, a comparative incidence not having been established as yet; 2) the absence of early symptomatology; and 3) the possibility that, in the late stages of the disease with metastases, confusion may arise as to the origin of the primary growth for the adrenal is often the site of metastatic deposits from carcinomata of other organs.

The nonhormonal type of adrenal malignancy is usually discovered in its late stages when it becomes manifest by the presence of a definitely palpable mass, vague abdominal and flank pains, malaise, diminution of appetite, and, like a silent hypernephroma, by signs and syptoms due to a metastasis in the lung or some other organ. The duration of symptoms ranges from 8 months to 2 years with an average of 1 year. These neoplasms are seen practically only in adults over 30 years of age and without predilection for either sex (Cahill, Hartung, Macera, Stevens, Gibson, Loeb, etc.).

The diagnosis of adrenal cortex disturbances has been greatly facilitated by the recent advances in endocrinology, 17-ketosteroid urinary excretion studies, and the studies in electrolyte and vitamin C balances (Beall, Beall and Reichstein, Grollman, Soffer, Szent-Gyorgi, etc.). Of greatest aid, especially in hormonal tumors, has been the introduction of perirenal insufflation of air by Carelli, and its popularization and simplification by Cahill and Mencher. This procedure, in conjunction with excretory urography and laminography, is of inestimable value in the diagnosis and localization of diseases and neoplasms of the retroperitoneal organs.

Thus far, the treatment of nonhormonal malignancies has been surgical extirpation, when possible, followed by high voltage irradiation to the operative site and to metastases, as they arise. Three operative approaches have been used for adrenal tumors: 1) extraperitoneally, through a lumbar incision; 2) transthoracic; and 3) transperitoneal. Cahill prefers the last, claiming it affords the best exposure and permits of ligation of the pedicle before the tumor is manipulated. Young and Crile preferred the lumbar route, and Broster, the transthoracic.

The prognosis of the nonhormonal neoplasms is poor because they attain large size and often metastasize before presenting any symptoms. Of Cahill's 4 cases, reported in 1942, one died 11 months after operation; one was admitted in a moribund state with widespread metastases; one had a metastatic tumor, 2 years after operation, involving the aortic glands and inferior vena cava, but died 6 months later of peritonitis due to perforation of a sigmoid diverticulum; and the fourth was but 2 months postoperative. Roome's patient died shortly after operation. Loeb's patient was presented in 1941, 2 and ½ years after operation with metastases present. Gibson's case died postoperatively after an unsuccessful attempt to extirpate the mass, and at autopsy pulmonary metastases were found. Stevens' patient died 8 weeks after operation with metastases in the liver and lungs. This patient is the youngest, a 17 year old male with a 22 month history. The tumor, however, was not a clear-cut nonhormonal type for he presented certain features, such as pigmentation, usually associated with the hormonal type of neoplasm. Timoney's patient had an enormous nonmalignant adenoma.

It is not within the scope of this presentation to discuss etiology, physiology, pathology, etc. of these neoplasms. Their features are ably set forth in the paper of Cahill, Melicow and Darby, and in the monographs of Grollman and Soffer. We wish to present a case of nonhormonal carcinoma of the adrenal cortex in which metastases were discovered about 2½ years after surgical extirpation and the patient is still alive and comfortable 5 years after the procedure. The patient also presented a marked hypertensive state which was permanently alleviated after removal of the neoplasm and homolateral kidney.

CASE REPORT

B. G., Jewish Hospital of Brooklyn, No. 254352, a 50 year old Russian Jewess, was admitted to the gynecological service on May 26, 1942 with the chief complaint of "falling of the womb." This condition had been present for several years. In addition, she also had episodes of rectal bleeding and tenesmus. There was no history of urinary disturbance. She was a gravida 9, para 3, and her last mentrual period occurred 1½ years ago. The rest of her past and familial histories was essentially negative.

Abdominal palpation revealed the presence of a large, hard mass that filled the entire right side and flank. It extended from underneath the costal margin to a short distance below the iliac crest. The liver seemed separate from and anterior to this mass. The liver edge was palpable 10 cm. below the costal border. The mass moved but slightly with respiration. Vaginal examination disclosed a relaxed introitus, a large rectocele, and a smooth, atrophic cervix. The uterus was small and the adnexae normal. There was no cervical, submaxillary, axillary or inguinal lymphadenopathy. Temperature was 99.8 F, pulse 88 and respirations 24. The blood pressure was 290/170 and ranged between 250/140 to 264/116 to 190/122 to 184/154 to 178/140 during the preoperative period.

Laboratory examinations: Urine alkaline, specific gravity 1013, albumin 2 plus, glucose 0, microscopically negative, culture negative. Hemoglobin 74 per cent, erythrocytes 3,680,000, leucocytes 6,500, polymorphonuclears 68 per cent, bands 5 per cent, lymphocytes 25 per cent, monocytes 2 per cent. The Kline test was negative. The sedimentation rate was 63 mm. in 1 hour. Blood chemistry:

Sugar 91, urea nitrogen 19 2, phosphorus 4.2 and sodium 306 mg. per 100 cc. An electrocardiogram showed a sinus tachycardia and left axis deviation.

An x-ray showed the presence of a large mass in the right upper quadrant. Excretory urography revealed the pelvis and calyces of the right kidney to be depressed and deformed with the pelvis at the level of the fourth and fifth lumbar vertebrae. Left urinary tract was normal in appearance. There was a calcific shadow just to the left of the midline between the left eleventh and twelfth ribs (fig. 1, *A*). A barium enema showed evidence of extrinsic pressure on the hepatic flexure and right half of the transverse colon.

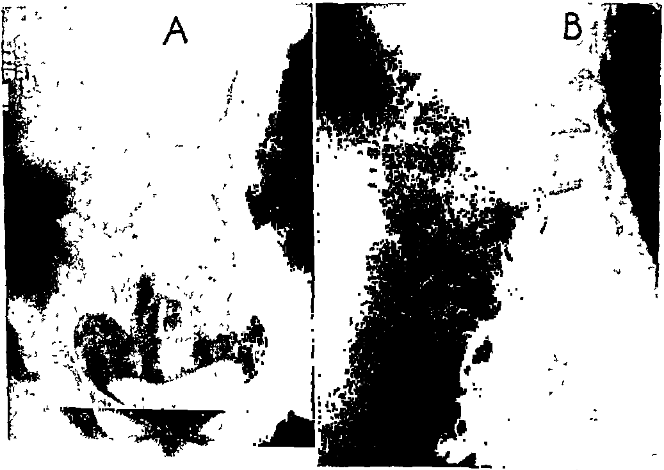

FIG. 1. *A*, Preoperative urogram. Right renal pelvis is depressed to the level of fifth lumbar vertebra, rotated medially and deformed by enormous mass occupying entire right side of the abdomen. Gall stone can be seen to left of the twelfth thoracic vertebra. *B*, Right lateral retrograde pyelogram. Thinned, compressed pelvis and calyces are extending far anterior to fifth lumbar vertebra.

Cystoscopy on June 5, 1942 showed mild cystitis and trigonitis. Indigo carmine retruned in 5 minutes in 4 plus concentration from both sides. A 5F ureteral catheter was passed up the right ureter but met an obstruction at 19 cm., although a flow of clear urine was obtained. A retrograde pyelogram was made with 48 per cent hippuran solution. This confirmed the excretory urogram, and a lateral projection showed the pelvis to be displaced far anteriorly (fig. 1, *B*). The calcific shadow was visualised in the anterior abdomen and believed to be a gall stone in a displaced gallbladder.

The preoperative diagnosis was right renal neoplasm. On June 6, 1942, with the patient under nitrous oxide-ether-oxygen anesthesia, through a curved right loin incision, 25 cm. long, a very large, firm mass was found within Gerota's fascia. Numerous dilated veins, ranging up to 1 cm. in diameter, coursed over its surface. The twelfth rib was cut but not removed. The upper pole of the tumor was markedly adherent to the diaphragm, and, in freeing it a rent was made in the pleura. This was immediately repaired and protected by packing. Another opening was inadvertently made in the peritoneum, through which the liver was explored and found to be free of metastases. The gallbladder, which with the right lobe of the liver had been displaced anteriorly and to the left by the mass, was found to contain a large calculus. This accounted for the calcific shadow seen to the left of the midline on the radiographs. The peritoneal rent was repaired after the anterior surface of the mass had been freed. After delivery of the upper pole of the mass, the kidney was exposed, attached to the mass and lying anteriorly to it. The kidney was also rotated on its transverse axis. The patient's condition became grave, and rather than tediously dissect the neoplasm from the kidney, it was deemed best to do a nephrectomy. The mass and the kidney were removed in toto. The postoperative diagnosis was adrenal neoplasm.

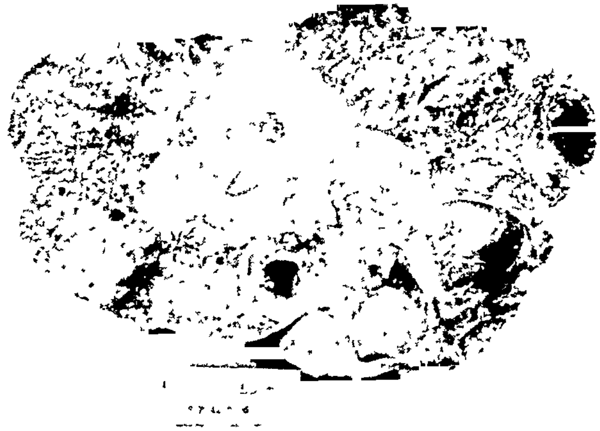

FIG. 2. Gross specimen. Variegated appearance of cut section of tumor. Mixture of solid, cystic and hemorrhagic areas.

Pathological report (Dr. D. M. Grayzel): The right kidney measured 11 by 6 by 2.5 cm. and weighed 152 gm. The attached mass measured 23 by 12.2 by 8 cm. It did not involve the renal parenchyma. The external surface was lobulated and was red-grey and brown in color. The consistency was mostly firm, but soft and cystic in areas. Stretched over the surface, in one area, was a band of bright yellow-brown tissue 14 cm. in length. This merged indistinctly with the tumor mass. On section, a variegated appearance was presented. Most of the tumor consisted of grey-brown elastic tissue arranged in a lobulated fashion. The central portion was composed of gelatinous yellow-grey material as well as irregular cysts measuring up to 4 cm. in diameter and filled with muddy red-brown material and friable, soft, grey-green tissue. In some places, areas of hemorrhage, up to 3 cm. in diameter, were seen (fig. 2).

Microscopic examination: In some areas, the cells appeared to be mounted in many rows, on delicate connective tissue stalks with vascular cores. In other areas, the cells were in nests and sheets enclosed by delicate bands of collagenous tissue. In still other areas, the cells tended to arrange themselves about irregular lumina. The cells were large with marked variation in size and shape. The cell outlines were distinct, the cytoplasm abundant, granular, or foamy, and occasionally clear. The nuclei, in many, were round or oval, and vesicular with prominent nucleoli. In others, the nuclei were hyperchromatic and bizarre-shaped. Some were in mitotic division. Giant tumor cells were also seen in scattered areas. There were many engorged capillaries and venules containing tumor cells. In other preparations the tumor cells were seen about nerve bundles. In one preparation, bordering the tumor and well demarcated from it by a connective tissue capsule, there was a narrow band of adrenal gland tissue, which showed both cortical and medullary zones. The cells appeared well preserved. Preparations from the kidney showed nothing of note. Diagnosis: Adenocarcinoma of the adrenal gland (fig. 3).

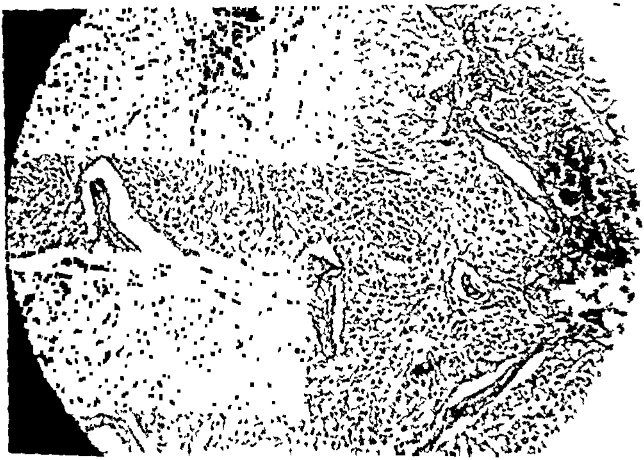

Fig. 3. Microscopic section under high power. Large cells with distinct outlines and large nuclei. Tumor thrombi present in vessels.

Convalescence was somewhat stormy. The patient received desoxycorticosterone acetate, glucose and saline infusions, blood and sulfadiazine. Right basal pneumonitis developed. The temperature ranged about 101° F during the first week and then gradually subsided. She was discharged on the thirtieth day after operation. Urinary hormone studies on the fifteenth day showed the following: Prolan, negative; estrin, 14 rat units; androgen, 2.8 mg. in 24 hours, all within normal range. Her blood pressure, postoperatively, ranged from 130/100 to 170/80 to 140/100 to 160/84 to 124/90 to 154/98 to 124/80 to 136/76.

The month following operation, the author entered the armed services and, upon resuming his civilian status 41 months later, was most pleasantly surprised to find the patient alive and apparently in good health. She had received a course of radiation therapy to the operative site and abdomen, starting on July 28, 1942, consisting of 2500 r to each of 4 fields for a total of 10,000 r. On January 19, 1943, a chest radiograph was negative for metastases. On March 26, 1945, 33 months after operation, a mass was felt in the right midabdomen, the size of a fetal head. Another course of therapy was administered of 200 r daily to two alternate fields for a total of 4000 r. On May 21, 1945, the mass was found to have maintained its size and the last course of therapy was repeated. The conclusion of this treatment found no diminution in size of the metastasis but the patient had lost 18 pounds in weight. Examination on September 14, 1945 revealed the presence of a large mass filling the left upper quadrant and the first mid-abdominal mass now had a companion to its left. Radiation therapy was now started to each of 8 portals, 4 anterior and 4 posterior, in daily dosage of 200 r to a total of 1600 r to each field. On October 4, 1945, 39 months after operation, x-ray of the chest revealed, for the first time, a right superior mediastinal para-aortic mass 8 by 4 cm. in diameter (fig. 4, *A*). On February 18, 1946 treatment was started to anterior and posterior chest portals in doses of 150 r to a total of 1500 r per portal. An excretory urogram, on December 24, 1945, revealed normal function of the left urinary tract and without any deformity of the pelvis and calyces.

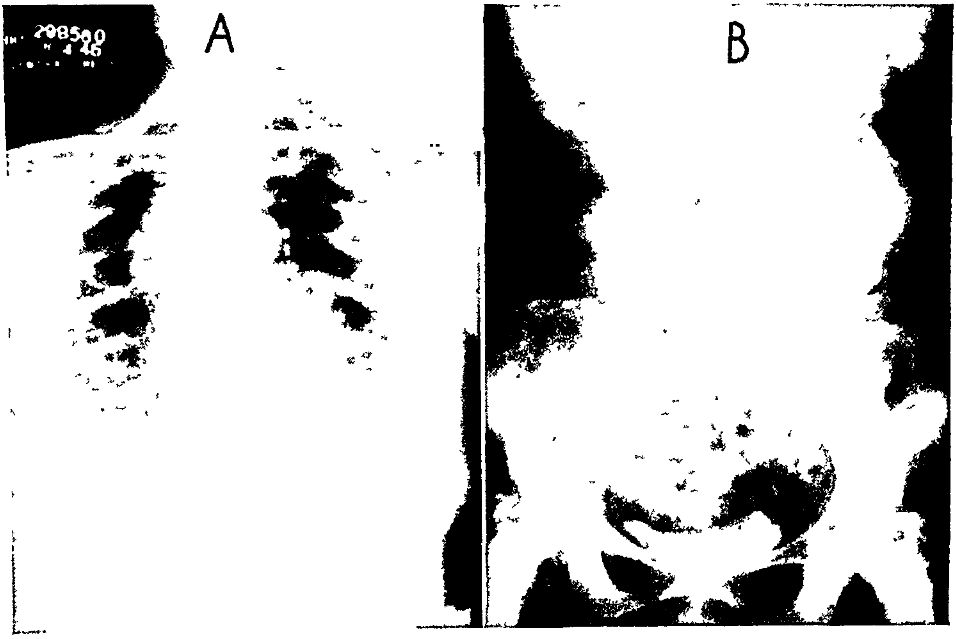

FIG. 4. *A*, Pulmonary and mediastinal metastases first noted October 4, 1945, thirty-nine months after operation. *B*, Excretory urogram 50 months after operation. Compare with figure 1. Left renal pelvis markedly displaced and rotated. Gall stone now seen in right upper quadrant.

The patient's general condition was good and she continued doing her own housework. She was comfortable despite the presence of the metastases. On September 30, 1946 she was re-admitted to the hospital. Her blood pressure ranged from 150/90 to 114/64, averaging 120/80 An excretory urography revealed considerable displacement of the left renal pelvis by an extrarenal mass (fig 4, *B*) The urea nitrogen was 19 2 mg per cent The phenolsulphonphthalein excretion was 65 per cent in 2 hours Hormonal assays, androgen and estrogen, were within normal range for a female of her age The potassium tolerance showed a failure of a rise in blood level, a finding associated with adrenal cortical neoplasms.

At the present date, 5 years of observation postoperatively have been concluded Her general condition can be considered good for she is fairly comfortable, ambulatory, continues her household duties and requires no analgesics nor sedatives Her blood pressure continues at a level of 120/80 There is no diminution in the size of the metastases, but no others have appeared either clinically or radiologically

DISCUSSION

This case is illustrative of the insidious onset and progression of nonhormonal adrenal cortical carcinomas Had not the patient entered the hospital seeking surgical relief for a rectocele, the presence of the neoplasm might not have been ascertained until after metastases had appeared This is a vivid example of the desirability of regular, thorough physical examinations if our campaign against cancer is to be effective

The correct preoperative diagnosis of an adrenal neoplasm should have been made, had we considered its possibility and employed perirenal air insufflation The presence of the enormous mass, the pyelographic deformity, and, as stated in our introductory remarks, the absence of the dramatic changes associated with the hormonal type of adrenal tumor, influenced us to consider this as a renal neoplasm We have now become adrenal-conscious and have performed perirenal insufflation frequently and successfully since then

There are 2 remarkable features in this case. One is the attainment of a 5 year survival period despite the presence of extensive abdominal and mediastinal metastases The patient is comfortable and it is possible that she may continue so for several more years before deterioration or spread to some vital center takes place We have found no report of a similar survival. The effectiveness of the radiation therapy cannot be fully evaluated for these neoplasms are classified as being radio-resistant Furthermore, the metastatic deposits apparently did not respond by receding or even slightly diminishing in size.

The second remarkable feature is the reduction of the severe preoperative hypertension to normal levels and the maintenance of this reduction over a 5 year period of observation We believe that the hypertension was caused by torsion of the renal pedicle due to the depression and rotation of the kidney by the tumor. This probably caused a partial ischemia of the kidney as observed in Goldblatt's phenomenon As Selye has demonstrated experimentally, interference with the vascular supply of one kidney, where its mate is normal, causes the formation of pressor substances with a resulting hypertension which can be relieved by removing the diseased organ An adrenal hormonal etiology for the hypertension in this patient can be eliminated by reason of the persistence of the postoperative reduction to normal levels despite the presence of extensive metastases. Thus, to the slowly growing list of cured cases, observed for 5 years, of hypertension caused by unilateral renal disease, we add one caused indirectly by torsion of the renal pedicle due to the pressure of a very large adrenal neoplasm. What might have been the effect upon the hypertension had we but removed the mass and preserved the kidney is highly speculative. Now, that a metastatic mass in the left renal area is causing marked distortion of the left kidney, it will be extremely interesting to note what effect this will have on the blood pressure in the future.

SUMMARY

A case of nonhormonal adrenal cortical carcinoma is presented in detail because of some very interesting clinical features. The patient has attained 5 years survival in comfort, although extensive mediastinal and abdominal metastases have been present for at least the past 27 months. This is the longest reported survival of a patient with this type of neoplasm. Severe preoperative hypertension has been reduced to and maintained at normal blood pressure levels as proven by 5 years observation following successful extirpation of the original growth and the affected kidney. This adds another etiological factor to the causes of hypertension in unilateral kidney disease.

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MANAGEMENT OF THE INJURED KIDNEY PRELIMINARY REPORT[1]

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During the period from October 1940, when the Charlotte Memorial Hospital was opened, to June 1947, a period of approximately 7 years, 23 cases of renal injury were admitted to the Charlotte Memorial Hospital Thirteen were classified as ruptures, 12 proven by x-ray or operation, the other died of shock shortly after admission One was a stab wound, and the remaining 9 cases were classified as contusions These figures closely correspond to those of Wood who reported 25 cases admitted to the Brady Urological Institute of the Johns Hopkins Hospital during the 6-year period 1929 to 1935 This series contained 11 ruptures, 2 lacerations, and 12 contusions In our series, 7 cases or 30 per cent were operated upon, while in Wood's series 13 cases or 52 per cent were submitted to surgery If all of our rupture cases had been operated upon, our percentage of surgical cases would have been 57 per cent Campbell and Osgood reported 52 cases admitted to the Bellevue Hospital during the 16 year period 1914 to 1929, 11 cases or 21 per cent of which were operated upon In our series there were 3 deaths, 1 due to shock shortly after admission, 1 due to shock 18 hours following admission and approximately 1 hour after a nephrectomy had been performed, and 1 due to an associated head injury on the tenth hospital day This gives a mortality of 13 per cent as compared to 12 per cent in Wood's series and 34 per cent in the series of Campbell and Osgood

Of the 23 cases, 11 were injured in vehicular accidents, 7 in industrial accidents, 3 in athletics, and 2 by weapons Of the 11 in the first group, 6 were in automobile accidents, 4 were hit by automobiles, and 1 was run over by a farm wagon Of the 7 industrial accidents, 3 were hit by boards thrown from ripsaws, one by a flying instrument in a mill, one fell from a boxcar, one from a truck, and one 14 feet down a coal shute Of the 3 athletic injuries, one was received while playing football, one while sledding, and one was caused by a fall from a tree The 2 penetrating wounds were caused by a pistol bullet and by a knife

The time expiring from the occurrence of the injury to admission to the hospital varied from 30 minutes to 10 days Thirteen were seen less than an hour following injury, 3 in less than 24 hours, and 7 between 3 and 10 days following the injury The 3 cases in which death occurred were all seen less than 30 minutes following the accident

SYMPTOMS

Pain was the presenting symptom in 83 per cent of the 23 cases Fifty-three per cent of those having ruptures complained of severe pain on admission as compared to 11 per cent of those having contusions Thirty-eight per cent of those having ruptures and 55 per cent of those having contusions had pain which was classified as moderate. This gives a total of 91 per cent of those having ruptures as compared with 66 per cent of those having contusions. Only 1 case with renal rupture had no pain. In this case, the injury preceded admission by 10 days, and the patient admitted that he had considerable pain for several days following the injury.

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[1] Read at the Annual Meeting of the North Carolina Urological Association, Sedgefield, N. C, October 6, 1947

SIGNS

Hematuria. All of the 23 cases presented hematuria, 21 of them gross and 2 microscopic. The 2 cases having microscopic hematuria were both cases of contusion, but it does not follow that mild or microscopic hematuria indicates a mild lesion, for a complete rupture of the vascular pedicle may result in no hematuria at all until the process of infarction begins.

Tenderness. Seventy-nine per cent of those having ruptures and 77 per cent of those having contusions were found to have tenderness in the flank on physical examination. Sixty-one per cent of those having ruptures were exquisitely tender as compared to 33 per cent of those having contusions. Only 3 cases with renal rupture did not have tenderness; in 2 of these 4 and 7 days respectively had elapsed between the injury and admission, and the third was a man who had been shot with a pistol only 30 minutes prior to admission.

Rigidity. Examination revealed rigidity on the affected side in 69 per cent of those having ruptures and 22 per cent of those having contusions. Only 4 cases with renal rupture did not show rigidity; in 3 of these 6 to 10 days had elapsed since injury and the fourth was the bullet injury case.

Mass. Four or 31 per cent of the cases with rupture of the kidney presented a palpable mass in the flank on physical examination.

Shock. Fifty-three per cent of the cases with rupture and 33 per cent of the cases with contusion were in mild to severe shock on admission to the hospital. Of the 6 cases of renal rupture which did not show signs of shock on admission, from 3 to 10 days had elapsed in 5 cases and one had been injured less than 30 minutes previously.

ASSOCIATED INJURIES

In 2 of the 23 cases, there were fractures of one or more ribs on the injured side. There was a fracture of the radius and ulna in one and of a digit in another. There were 3 cases of intracranial injury, one of whom expired from this associated injury. There was one in which the liver was thought to be damaged. This case expired shortly after admission of shock and an autopsy was not obtained.

It is perhaps superfluous to add here that when one is dealing with a case having an associated injury of severe nature, such as a serious head injury, one cannot follow the routine of investigation which I will propose later in this paper but must act conservatively and in co-operation with the general surgeon or neurosurgeon as the case may be. Preservation of the patient's life is of paramount importance in these cases, proper management of the injured kidney secondary.

X-RAY EXAMINATION

Flat film. A flat film of the abdomen was taken on all but 4 cases. The psoas muscle shadow was obscured or obliterated in all 7 of the cases operated upon and in 3 cases which were treated conservatively.

Excretory urography. Intravenous studies were performed on 15 of the 23 cases. Diagnosis of rupture was made clinically in 3 cases in which excretory urography was not utilized. Two of these were operated upon soon after admission, the other died of shock shortly after admission. In the 15 studies made, there was no function from the injured side in 2 cases, poor filling in 7, and good filling in 6. In 1 case in which there was poor filling there was slight but definite extravasation of the dye for a short distance outside of the calyces but not beyond the capsule. This case will be discussed later. In 2 of the cases in which there was good function there was marked extravasation of the dye outside of the renal shadow.

Retrograde pyelography. This was employed in only 3 cases. In 2 cases there was extravasation of the dye. The use of this diagnostic aid in cases of renal injury is very controversial and will be discussed later.

TREATMENT

Of the 23 cases, 7 were operated upon, 4 soon after admission, 1 the day after admission, one 2 days after admission and one 10 days after admission. Nephrectomy was performed in 4 cases, 2 cases were evacuated of blood clots and drained, and in one case the rupture was repaired and drained. This case is reported below. Six cases diagnosed as rupture were not operated upon. One of these expired of shock shortly after admission.

Case report. S. A. W., CMH No. 61425, a 10 year old white boy, was admitted to the hospital on March 5, 1947, three days following a sledding accident. He had gross hematuria and severe pain in the right side which subsided to a dull ache. He was referred to the hospital only when chills and fever developed. On admission to the hospital, his temperature was 101.0 degrees F., pulse 88, respirations 20, blood pressure 122/10. The right flank was exquisitely tender and rigid, and there was a palpable mass. The abdomen was soft and nontender. His urine was grossly bloody. The white blood count was 11,850 with 80 per cent polymorphonuclear leucocytes. The red blood count was 4,150,000, the hemoglobin was 11.0 gm. or 76 per cent. Excretory urograms were made immediately following admission. The flat film showed the psoas and renal shadows on the right to be obliterated. There was only very slight excretion of the dye on the right side in 20 minutes, the left was normal. A preoperative diagnosis of rupture of the right kidney was made, and the patient was operated on approximately 1 hour after admission to the hospital and 72 hours following his injury. On exploration through a flank incision an estimated 200 cc. of dark blood clots mixed with small bits of necrotic fat tissue were evacuated from beneath Gerota's fascia. The kidney was delivered and a deep laceration near the upper pole was found which extended about one half way down to the pedicle on both surfaces of the kidney (fig. 1). The kidney was of good color except for a narrow border of pale white tissue at the edge of the laceration. There was no active bleeding from these surfaces. No calyx was identifiable in the depths of the rupture. The pedicle vessels were found to be intact. Three thicknesses of hemostatic oxycellulose gauze were placed in the rupture and the edges of the cortex were approximated over this by several interrupted sutures of 0000 chromic catgut which were placed through the capsule only. A short pyelotomy was made, through which a blood clot was evacuated from the pelvis of the kidney. The wound was closed over 3 Penrose drains. The patient was given 500 cc of whole blood and 450 cc of 5 per cent glucose in normal saline during the operation and left the table with a systolic blood pressure of 130 mm. of mercury. His post-

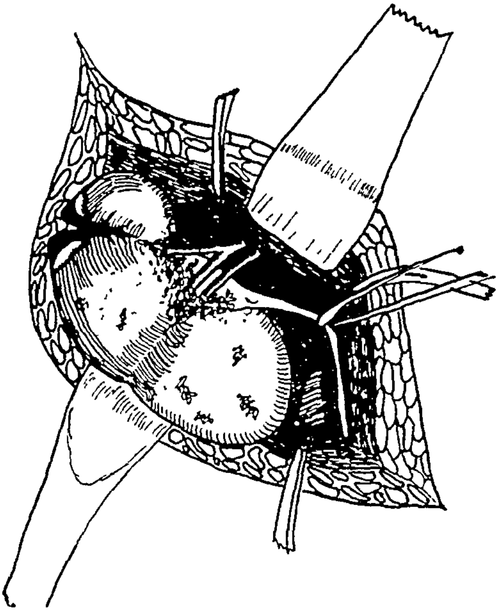


Fig. 1. CMH No. 61425. Sketch made at operation 72 hours following injury and showing cortical rupture and narrow area of cortical infarction at edges of rupture.

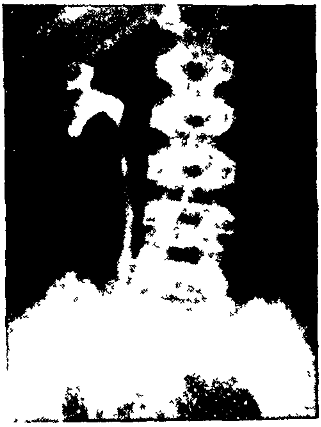


Fig. 2. CMH No. 61425. Retrograde pyelogram 6 months following injury and repair of renal rupture.

operative course was smooth and he was discharged ambulatory and with the wound healed on the 15th postoperative day On discharge, the urine contained only a few red and white blood cells per high powered field His urine had been kept acid with ammonium chloride to prevent stone formation, and he had been given 20,000 units of penicillin every 3 hours A retrograde pyelogram made 6 months after discharge shows no abnormality (fig 2) The renal shadow terminates abruptly above the superior calyx indicating that the superior one fifth of the kidney has atrophied Urine from the kidney was negative on microscopic examination There was an appearance of phenolsulphonphthalein from the No 4 ureteral catheter in 8 minutes and an excretion of 10 per cent of the dye in a 10 minute specimen

Comment MacDonald and Matthews have experimentally demonstrated on dogs that Fibrin Foam and Gelfoam used in a similar manner to which we used the oxycellulose gauze give a narrow scar with little or no sclerosis of the surrounding renal parenchyma

LATE SEQUELAE

The ruptured kidney which is not explored and either removed, repaired, or drained is subject to a number of sequelae Wood lists these as secondary hemorrhage, extravasation of urine, infection, hydronephrosis, calculous formation, and calcified cysts of the kidney Stirling and Lands state that while the majority of injuries of the kidney heal spontaneously, the organ may later become functionless as shown by subsequent functional and pyelographic studies They mention a case on which an excretory urogram, made 8 weeks after expectant treatment, showed partial atrophy of the kidney with the lower calyces almost obliterated They believe that early drainage probably would have saved the function of the kidney Campbell and Osgood state that an extensive tear of the kidney substance may heal but does so with the formation of a dense scar so that a considerable portion of secretory tissue may be destroyed, or a part of the kidney may suffer from insufficient blood supply due to the scar formation and subsequently atrophy They found that patients treated conservatively were apt to be confined for long periods and not only subject to late hydronephrosis, cystic degeneration, nephrosclerosis, perirenal sclerosis and calculous formation, but likely to have disabling pain requiring late nephrectomy for relief Lowsley and Kirwin likewise emphasize that the remote possibilities of kidney injury must be considered They believe that destruction of renal parenchyma may lead to permanent loss of function, and that in healing the cicatricial distortion of a calyx or of the pelvis may lead to hydronephrosis Colston and Baker, in considering the later sequelae of renal injuries, found that of 13 cases, 6 later had cyst formation Colston reported a huge calcified renal cyst following injury of the kidney Bell had 2 cases which he treated conservatively by bed rest for 3 weeks Both patients complained of pain at the onset which subsided to a dull ache subject to acute exacerbation during the years following the injury. Both remained in poor health until nephrectomized X-rays showed calcification in the area of extravasation in one case and stones in the calyceal system in the second. At operation both kidneys were found to be totally destroyed. Cumming and Schroeder reported a case of a 22 year old female who had been stepped on by a horse 17 years previously and had hematuria following the injury. The pyelogram showed a distorted pelvis with only 2 calyces which were small, extremely narrow, and blunted, the lower of which contained a sizeable calculus. The dye function was poor with a delayed appearance time. Wood, in his series of 25 cases of renal injury, reported formation of a stone in one, loss of 60 per cent function in a second with no filling of the middle and inferior calyces on excretory urography, and formation in a third of a cystic mass the size of a cantaloup which on operation was found to be filled with urine. Dr. William Coppridge has kindly allowed me to show slides of the x-rays of a case of his. The patient was admitted in mild shock following an automobile accident. The urine on admission contained 1–3 white blood cells and an occasional red blood cell per high powered field. The initial retrograde pyelogram was made 16 days following the injury (fig. 3, *A*) and shows parenchymal extravasation of the dye. This was repeated 3 days later with the same findings and there was no excretion of dye in 15 minutes. A retrograde study made 6 months following the injury shows virtually complete atrophy of the kidney (fig. 3, *B*). The renal outline is reduced

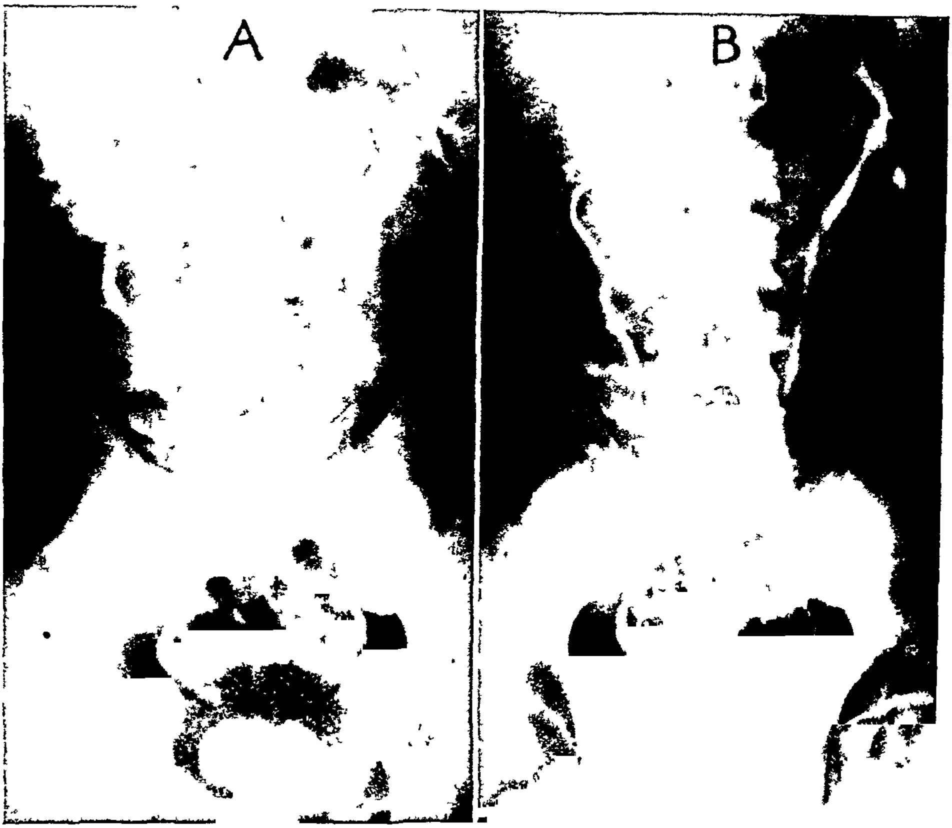


FIG 3. Case of Coppridge *A*, Retrograde pyelogram 16 days following injury, showing parenchymal extravasation of dye on right side. *B*, Retrograde pyelograms 6 months following injury, showing atrophy of right kidney.

to $1\frac{1}{4}$ inches by $1\frac{1}{2}$ inches The kidney was functionless A repeat examination 4 years following the injury shows no change We believe that this case represents an injury of the vascular pedicle of the kidney with subsequent occlusion of the blood supply

An effort has been made to locate the 5 cases in our series in which rupture of the kidney was demonstrated by x ray but operation was not performed However, we were successful in obtaining a follow-up study in only 1 case

Case report L M B, CMH No 55139, a 26 year old housewife, was admitted to the hospital on August 17, 1946, seven days following an automobile accident, because of persistent hematuria and kidney colic on the left side of 4 days' duration associated with urgency and frequency She denied having any symptoms referable to the urinary tract prior to her injury Her temperature was 99 8 degrees F, pulse 92, respirations 22, blood pressure 118/76 There was no tenderness, rigidity, or mass in the abdomen or flank The urine was grossly bloody, red blood count 4,150,000, hemoglobin 80 per cent, white blood count 16,800 A flat plate of the abdomen revealed an indistinct left psoas outline Excretory urography revealed poor function on the left side with poor filling of the calyces and a very slight extravasation of the dye from the superior calyx into the parenchyma Two days following admission the urine contained 5–8 red blood cells and 10–15 white blood cells per high powered field She was given a total of 640,000 units of penicillin, and on discharge 4 days following admission the urine was free of microscopic elements, and she was asymptomatic and afebrile She returned for a check-up examination on September 5, 1947 She had no complaints The urine contained 10 white cells per high powered field, and a stained smear showed numerous bacilli There was an appearance of the phenosulphonphthalein in 12 minutes from the left side with an excretion of 10 per cent in 20 minutes A retrograde pyelogram was somewhat blurred but shows dilation and blunting of the superior and inferior calyces and apparent constriction of the middle calyces (fig 4) A repeat examination could not be obtained

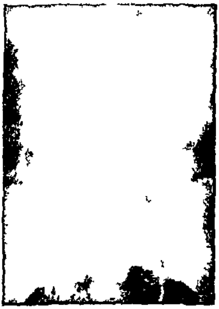
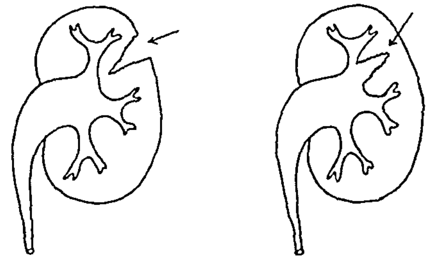


FIG 4 CMH No 55139 Retrograde pyelogram 1 year following injury, showing clubbing of some calyces and constriction of others

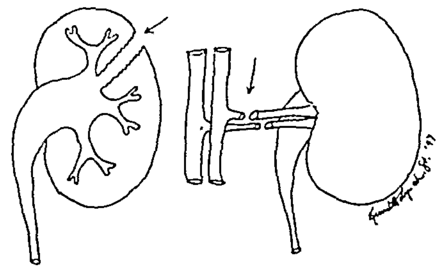
DISCUSSION

Numerous others have adequately described the various types of rupture which may occur. I merely wish to point out that four general types should be kept in mind (fig. 5). They are ruptures confined to the calyceal system, rupture confined to the cortex, communicating rupture, and rupture of the vascular pedicle.

Good management of any renal disease is that which in the end will conserve renal tissue. Conservation of the injured kidney depends first on the early diagnosis of rupture of the kidney parenchyma if such is present. Typical symptoms and signs referable to the flank as pain, acute tenderness, rigidity, a palpable mass, shock, and hematuria following trauma should be diagnostic in itself. In other cases where the clinical picture is not so clear, a flat x-ray film of the abdomen and intravenous urography should be performed as soon as possible. Obliteration of the psoas muscle shadow in acute injuries is evidence of extrarenal hemorrhage, provided there is no history of pre-existing renal disease. When there is poor excretion of the dye on the injured side, retrograde pyelography will give indisputable evidence of rupture of the calyceal system. Sargent believes that retrograde studies should be performed in all such cases. A great many urologists are prejudiced against the use of the retrograde pyelogram in the injured kidney. They believe that injection of the dye may incite new bleeding, may be an irritant to the ruptured parenchyma, and may disseminate infection. No evidence which would indicate or prove that the bleeding will be aggravated has been found in the literature. However, it would seem advisable to be prepared to explore the kidney should a rupture be demonstrated and hemorrhage ensue following injection of the dye. Furthermore, the patient may be transfused in such an eventuality. That skiodan acts as an irritant on the renal parenchyma



Rupture of capsule Rupture of pelvis



Complete rupture Rupture of vascular pedicle

FIG. 5. Four types of renal rupture

has been disproved by a case of Campbell in which the kidney pelvis was punctured by the catheter in a routine retrograde study and the dye widely extravasated through the parenchyma We have had a similar case in which the catheter perforated to the capsule in a routine study and all of the dye extravasated beneath the capsule (fig 6) An excretory urogram performed 48 hours later showed complete absorption of the skiodan and an entirely normal pyelogram The patient had no pain, no tenderness in the flank, and no fever following this accidental rupture and extravasation of the dye In answer to the complaint that retrograde pyelography may disseminate infection, I can say only that most urologists believe that if there is extravasation of blood or urine, infection will usually arise even without passage of a catheter. In our series 3 cases of proven rupture in which the patients were not admitted to the hospital until 7 to 10 days following the injury were found to have numerous leukocytes in the urine although they had not been catheterized None of these admitted symptoms referable to the urinary tract prior to the injury

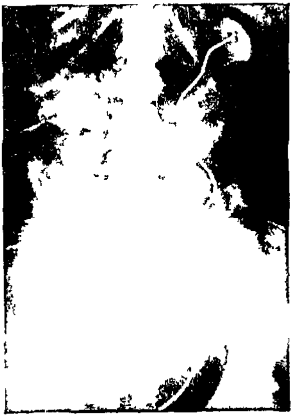


Fig 6 CMH No 62369 Retrograde pyelogram, showing extravasation of dye beneath capsule of normal kidney

I believe, as does Wood, that all ruptures of the kidney as established by flat film, excretory urography, or retrograde pyelography should be subjected to exploration Early exposure enables the surgeon to remove the extravasated blood clot which if allowed to remain may become infected or result in fibrosis Secondly, early exposure enables one to inspect the kidney and adjacent structures and make the necessary repair where possible, practicing conservative surgery Thirdly, early exposure enables one to perform a primary nephrectomy when indicated Wood believes that exploration is more easily carried out several days following the injury when the extravasated blood has coagulated and no active bleeding will be encountered There will be no appreciable extravasation of urine during this period as there is little or no renal function immediately following injury Furthermore, if infarction occurs, it should be visible on inspection of the kidney after 72 hours have passed, and the surgeon will be able to form a more accurate estimate of whether the kidney should be removed. With severe rupture, however, the patient may go into deep shock and expire, even with transfusions, and should therefore be operated upon as soon as possible.

SUMMARY

Twenty-three cases of injury of the kidney were analyzed statistically in regard to etiology, symptomatology, and presenting signs. All acute ruptures of the kidney were found to complain of severe pain, to have acute tenderness and rigidity of the flank, and in 31 per cent of the cases to have a palpable mass. Mortality figures were given. Operations performed in 7 cases were listed and one repair using hemostatic oxycellulose gauze was described.

Late sequelae of renal injury were presented and discussed.

Intravenous urography and retrograde pyelography were urged for complete and accurate evaluation of a case of suspected renal injury. The bugaboo of retrograde pyelography was discussed.

Exploration in all cases in which there is extravasation of intravenous or retrograde dye or obliteration of the renal and psoas shadows was advocated. Seventy-two hours was arbitrarily set as the ideal time to explore the kidney providing severe hemorrhage and shock do not require immediate operation.

I wish to express my appreciation to Dr. Hamilton McKay, Dr. Raymond Thompson, Dr. Preston Nowlin, Dr. Robert McKay, Dr. Walter Daniel, Dr. Aubrey Hawes, Dr. Brodie Nalle, Jr., and Dr. Haynes Baird of the urological staff and to Dr. E. P. Hipp, Dr. J. W. Gibbon, and Dr. J. P. Kennedy of the surgical staff of the Charlotte Memorial Hospital for permission to use their cases in this analysis. I particularly wish to thank Dr. Rudolf Bell and Dr. William Coppridge for permission to refer to their unpublished cases. I am also indebted to Mr. Rufus Meigs for the preparation of the illustrations.

This clinical analysis was carried out at the suggestion of Dr. Hamilton McKay. Since its completion we have managed a number of cases with injured kidneys according to the postulates set forth in this paper. We have obtained what we feel are very good results and plan to report these cases in the near future.

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MAJOR UROLOGICAL SURGERY ON POLIOMYELITIC PATIENTS CONFINED TO RESPIRATORS, DISCUSSION ON ETIOLOGY, PROPHYLAXIS AGAINST AND TREATMENT OF CALCULI IN RECUMBENT PATIENTS

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Prior to this publication, there are records of only 3 poliomyelitic patients with respiratory paralysis who survived any type of major surgery The first of these reports was by Gillespie in 1941 He recorded the details of a cesarian section on a pregnant women confined to a respirator because of infantile paralysis The mother survived the operation, but the child died 6 hours later from intracranial hemorrhage The operating time was 29 minutes Only local anesthesia was used The patient's respirations were carried out during the operation by fitting the mask of a gas machine on her nose and mouth, and administering pure oxygen through the induction bag Rhythmic pressure was made on the bag at the rate of 16 times a minute

Four years later, Metheny removed an appendix from a poliomyelitic patient who was in a Drinker respirator when she developed appendicitis The patient was anesthetized with nitrous oxide and a small amount of ether while still in the "iron lung" She was then slid out of the respirator and artificial respiration carried out during the operation by alternate pressure on the chest and on the re-breathing bag of the gas machine The operation was completed in 15 minutes and the patient returned to consciousness in satisfactory condition

In 1946, another cesarian section on a poliomyelitic patient in a respirator was reported by Strauss and Bluestone The pregnancy in this patient was further complicated by right pyelitis due to the colon bacillus and later by superimposed diffuse glomerulonephritis As the respirator could not be moved to the main operating room, an emergency operating room was improvised An endotracheal tube was passed The patient was removed from the respirator and maintained with a resuscitator until anesthesia was started Under cyclopropane insufflation anesthesia, with manual positive pressure to a re breathing bag, a classical cesarian section was done A healthy, 4 pound 5 ounce, premature female child was extracted The entire time, from incision to closure, was 25 minutes When the operation was completed, the Kreiselman apparatus was used until the patient was returned to the respirator The patient's immediate convalescence was satisfactory The child continued to gain in weight and at 4 months, weighed 9 pounds

The 2 patients whose histories we are about to summarize are, we believe, the first to be taken directly from the "iron lung" to the operating room and to survive major urological surgery Our cases have several other points of interest They emphasize to an unusual degree the danger of stone formation in recumbent patients They record our degrees of success in dissolving stones with solution G.

A 23 year old married woman, after 6 days of prodromal symptoms of poliomyelitis, was admitted on September 11, 1945, to Sydenham Hospital and later to the Respirator Center at Children's Hospital School. Examination showed complete paralysis of the upper right extremity and extensive paralysis of the left. There was marked weakness of both legs. Shortly after the patient was hospitalized, the diaphragm and intercostal muscles became involved. She began having serious difficulty in breathing and it became necessary to place her in a respirator.

From the onset of the illness there was difficulty in controlling the urine. Both voided and catheterized specimens soon showed large numbers of pus cells. Despite the administration of courses of sulfathiazole and sulfamerazine, the pus only decreased slightly in amount; it never disappeared entirely. Cultures taken at intervals showed colon bacillus and Streptococcus fecalis. The reaction of the urine remained alkaline, even though for a short time ammonium mandelate was prescribed.

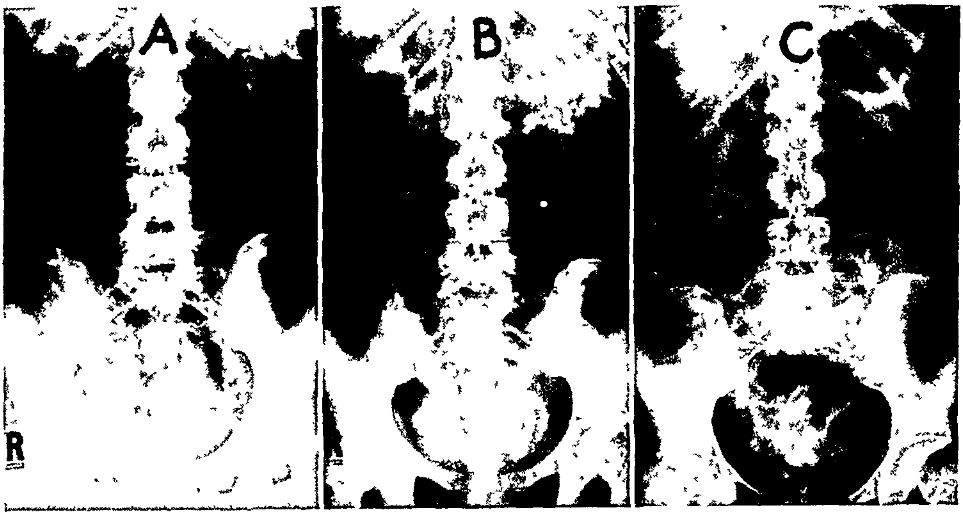

FIG. 1 Case 1. *A*, Numerous small stones in left kidney and ureter. *B*, Encrustations on bladder as well as numerous calculi in left kidney and ureter. *C*, Two large stones caught in lower end of right ureter. They were not seen in films taken 4 months previously Numerous calculi in left kidney seen in *A* and *B* have now been passed and bladder encrustations no longer are present.

After a month in the respirator, the patient began having less difficulty in breathing. She was able to be out of the "iron lung" for increasingly longer periods of time. By the sixth week she had regained sufficient power in her legs to walk with braces. However, there had been almost no improvement in the muscles of the upper extremity.

Although from the beginning of the illness the urine contained considerable pus, it was not until the eighth month that the patient complained of frequency of urination and pain on voiding. Plain x-rays were taken (fig. 1, *A* and *B*). They showed hundreds, actually thousands of small stones filling the left kidney and ureter, and encrustations over the entire bladder. At that time no stones were seen in either the right kidney or the ureter.

The phthalein output was only 25 per cent from the 2 sides for 1 hour; but an intravenous pyelogram was surprisingly good It showed only a slight hydronephrosis and hydroureter on the left The right kidney and ureter were well visualized and appeared normal Cystoscopy was done, but because of the marked bladder encrustations, it was impossible to pass a catheter into the left ureter A 2-way catheter was inserted into the bladder and continuous irrigation started (modified tidal drainage) At first boric acid was used and, after the patient became accustomed to this, solution G as advised by Suby and Albright

This measure was very successful in getting rid of the bladder encrustations, and at a second cystoscopy, it was possible to introduce a catheter for a few centimeters into the left ureter Ureteral and renal lavage were then started with solution G However, the catheter caused marked discomfort and slid out of the ureter in a few days, and so it is unlikely that solution G had any effect on the ureteral or kidney calculi In any case, shortly after this second cystoscopic examination, perhaps partly due to the dilatation of the lower end of the ureter, the patient started to pass stones and continued to do so daily, until within 2 months all the stones in the left kidney and ureter had been passed The fact that by now the patient was again able to stay out of the respirator at least part of the day and that we were making a point of having her sit erect for a short time every few hours, doubtless helped in enabling her to pass the calculi

Unfortunately, 10 months later the patient developed severe pain on the right side and x rays now showed 2 large stones caught low down in the right ureter (fig 1, *C*) These calculi did not show in the x rays taken 4 months previously, although they were probably there The left ureter and kidney, which 12 months before had been *filled* with calculi, now appeared normal

A cystoscopic examination was made and an unsuccessful attempt made to have the ureteral stones pass Her condition grew steadily worse, and the severe pain in the right side persisted It had now become necessary to keep her constantly in a respirator The nonprotein nitrogen increased The white count was markedly elevated Her temperature was 103 F, the pulse 120 Even though she now could not be outside of the respirator more than a few minutes without becoming cyanotic and losing consciousness, an operation was decided on

The anesthesia was administered by Dr Cless Fordyce who made the following record ' The respirator was transferred to the operating room and was kept in operation until time for the administration of the anesthetic Preparations had been made for intratracheal intubation in case it should be necessary Sodium pentothal (2½ per cent sol), which was supplemented by nitrous oxide and oxygen, had been chosen for the anesthesia The mechanism of the respirator was stopped and it was opened, giving access to an arm for the venipuncture and to the abdomen for the surgical procedure An assistant removed the heavy rubber collar from around the patient's neck When consciousness was lost, a face mask was applied and a flow of oxygen, 500 cc per minute and nitrous oxide 1000 cc per minute was started, using the absorption technique The patient's feeble respiratory efforts were supplemented by gentle, rhythmic pressure on the bag during inspiration After a few minutes, a pharyngeal airway was introduced without difficulty. A very light plane of anesthesia was maintained, which combined with the muscle paralysis gave very adequate relaxation. As soon as the operation was completed, the respirator was closed and its mechanism again started. The face mask was removed and patient was conscious within a few minutes."

A right inguinal extraperitoneal incision was made and continued around anteriorly almost to the midline. The upper of the 2 stones was easily removed, but great difficulty was encountered with the second. It was firmly wedged in the ureter a short distance from the bladder. Fifty minutes were required to complete the operation, the longest time recorded that a poliomyelitic patient with respiratory paralysis had been kept under an anesthetic. Nevertheless, the patient's condition was satisfactory at the end of the operation. A chemical analysis showed that the stones were composed entirely of ammonium phosphate. There were no traces of magnesium or of calcium.

The convalescence was stormy, but at the end of 2 months, the incision had healed and the patient had no urinary symptoms. As had been anticipated, when the urinary complication cleared up, her respiratory difficulty improved and she no longer needed the respirator.

This patient is now home and, while we realize there is danger of her developing further urinary complications, we are hopeful that the regimen now being followed will lessen this possibility. She has been instructed to force fluids, limiting herself, however, to 1 glass of milk a day so as to cut down her calcium intake. Attempts to keep the urine acid had never been successful in her case, doubtless due to the presence of urea-splitting organisms. With most of her infection cleared up, we may have more success with this in the future. She still can move her left arm only slightly and her right, not at all, but is again able to sit up and to walk with braces. She is encouraged to walk as much as possible and never to remain in the same position for a long period of time. In order to get all the advantages that different positions offer for urinary drainage, she has been instructed to lie on her face twice a day for half an hour. Regularly repeated roentgenograms, so far negative, will be continued.

The second patient was the sister of the first, 20 years old and weighing slightly more than 200 pounds. She was a student nurse at the time her sister was taken ill and was at once called home to assist in the nursing. Five days later, she herself developed poliomyelitis, with even more extensive paralysis than her sister. All four extremities were paralyzed along with the diaphragm and intercostal muscles. At Sydenham Hospital she was placed in a respirator and not until 2 months later could she remain out of it as long as an hour.

From the start of her illness, she complained of frequency of urination, although at first the urine contained no pus. After a few weeks, however, there was definite evidence of urinary infection, as shown by clumps of pus cells in the catheterized specimen. Cultures taken at different times during the year at Sydenham showed Aerobacter aerogenes, Streptococcus faecalis, and Escherichia coli.

The patient at one time complained of pain in the right flank, but plain x-rays and pyelograms taken 3 months after the patient was admitted to the hospital were negative, as was also a cystoscopic examination done at that time. She was given several courses of sulfadiazine and even streptomycin was prescribed. Each time she was helped symptomatically but the cultures remained positive.

At the end of a year she was transferred to Children's Hospital School. There had been almost no improvement in the muscles of either the upper or lower extremities, but the patient was able to be out of the respirator most of the time. During this year she lost over 100 pounds, which brought her weight down to only 95 pounds. An x-ray taken just the day before leaving Sydenham showed several large stones in the right kidney. She was then, however, having no pain.

The patient was cystoscoped at the Children's Hospital School; a catheter was passed into the right kidney and irrigation of the kidney pelvis with solution G started. We had little hope that solution G would dissolve such large stones, but preferred to try anything rather than surgery. Fluids were forced and when the patient could be out of the respirator, she was placed in a semi-sitting position. It was impossible for this patient to either stand or sit up straight.

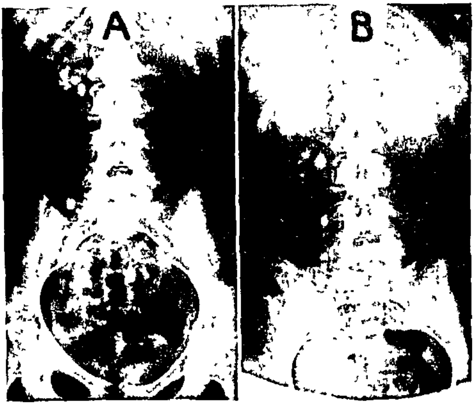

FIG. 2. Case 2. *A*, Large stone blocking lower end of right ureter and a group of large stones in right kidney. Left side of urinary tract negative. *B*, Several large stones blocking right ureter and several more still in renal pelvis.

Two months later, the patient developed severe pain in the right flank. An x-ray showed that one of the large stones in the right kidney had dropped into the ureter and apparently shut it off completely (fig. 2, *A*). The patient's condition became progressively worse, and she had to be constantly in the respirator.

An operation was decided on, and the stone was removed through a right low extraperitoneal incision. One might ask why was not the kidney explored at the same time and the renal calculi removed. Possibly this should have been done, but this girl was at best a very poor risk and both the anesthetist and the operator (Brady) believed that the minimum should be done with the maximum speed. An important factor that demands attention when major surgery is performed on paralyzed patients is the difficulty encountered in giving intravenous fluids. Because of the inaccessibility of the veins and their lack of tone, transfusions can usually be given only by cutting down on the vein.

For 6 days after operation, the patient was quite comfortable. Large quantities of cloudy urine poured out of the incision and she no longer had any pain. However, on the sixth day, the colic in the right flank returned and the urinary drainage through the incision stopped. An x-ray (fig. 2, *B*) showed that several stones had moved down into the ureter and again had blocked it. An immediate operation was necessary.

Because of the potential difficulty of keeping the patient breathing when placed in the usual kidney position, we were reduced to using an anterior approach. The peritoneum was once opened, but due to the atrophy of the muscles, it was possible to remain extraperitoneal during most of the operation. Very little kidney cortex remained. Several large stones were firmly wedged in the ureter. It was decided to remove the kidney and enough of the ureter to include all of the stones. This may seem radical, particularly as the patient is in danger of developing trouble in the other kidney at a future date, but we thought it the wisest procedure. When the removed kidney was inspected, we felt even more certain that a nephrectomy had been indicated. There was thick pus in the kidney pelvis and calcareous deposits in the calyces in addition to the large calculi. We do, of course, regret that we subjected this patient to 2 operations, but believe that she was in better general physical condition to stand a nephrectomy at the time of the second operation than she was at the first. These stones like those removed from her sister, were composed of phosphates, but in this patient the phosphates were combined with magnesium and only traces of ammonium and calcium were present.

Because of the infection, the wound took 6 weeks to heal. There is, however, no danger of hernia as this patient will never walk or sit up straight. She is still in the hospital, but quite comfortable and is on the regimen which we are carrying out on all the patients in the Children's Hospital School with any respiratory difficulty due to poliomyelitis. We feel that these measures are particularly indicated for those who are or who have recently been in the "iron lung."

We have at present in the Children's Hospital School, 8 patients in respirators. Their ages vary from 15 to 33. None of this group is having renal colic at the present time. All have had negative roentgenograms with the exception of one 17 year old girl who has some gravel in one of the calyces of the right kidney. Since we have recently been able to take her out of the respirator and have her sit up for hours at a time, we are hoping she will soon pass this. If she does not, we will introduce a catheter into the kidney pelvis and try to dissolve the calcareous material with solution G.

All except 2 of these patients can now be out of the "iron lung" for intervals varying from several hours to several days. As they become able to sit up and move around, the danger of stones forming becomes markedly decreased. It is in those who must spend all or a large part of their time in respirators that this danger is greatest In order to lessen this danger, the following measures are carried out on all patients in the "iron lung" unit of the Children's Hospital School

A daily fluid intake of at least 3000 cc is prescribed The dietician sees to it that there is a sufficient variety of food to ensure an adequate vitamin content In order to lessen the calcium intake, only 1 glass of milk a day is permitted Citrus fruits are given in only moderate amounts Alkaline drugs such as soda bicarbonate or alkaline saline cathartics are not used

The first morning specimen of urine is tested with nitrazine paper soon after it is voided If it is alkaline, ammonium chloride is prescribed for from 24–48 hours We realize that this will not acidify the urine when there is infection with urea splitting organisms and may even be harmful However, when this is not the cause, ammonium chloride may be very effective in lowering the pH A special reason for keeping the urine acid is that most of the stones in recumbent patients are made up of phosphates

Any complaints of frequency of urination or dysuria are investigated promptly When infection develops, which is an ever present danger, sulfathiazole or sulfadiazine is prescribed, but never for more than 1 week at a time We have not seen any cases where stone formation could be attributed to sulfonamides, but it would seem logical to suppose that in recumbent patients there would be an increased possibility of this occurring

When renal colic or any pain in the flanks is complained of, x rays are at once ordered Moreover, routine roentgenograms are taken at regular intervals As our first patient demonstrated, stones of considerable size can develop in recumbent patients in a very few months

We believe that nothing is more helpful in preventing the development of stones in recumbent patients than frequent change of posture While realizing the roles played by infection, decalcification of bones, the pH of urine, hyperparathyroidism, dietary deficiency, and probably several other factors, stasis is probably of prime importance in the formation of calculi in recumbent patients

Boyd demonstrated by stereoscopic pyelograms that in some patients there are major and minor calyces which are directly dorsal to the pelvis With a pelvis of this anterior variety drainage from the dorsal calyces is not free, and it is almost impossible to get rid of any gravel which may collect in them without turning the patient on her face He reported a case in which by placing a patient on her face for several hours a day, she was able to pass a large amount of gravel which had collected in both kidneys Boyd recommends that a patient drink large quantities of fluid before being placed in a prone position Pulvertoff also emphasized the importance of renal drainage in recumbent patients He insists not only that they be turned on their side several times a day, but also that they be tilted by alternately raising on blocks, the head and foot of the bed

It is difficult at best to see to it that paralyzed patients have their positions changed frequently When these patients have to spend all or a large part of their time in respirators, this feature becomes a nursing problem of major importance It is sometimes impossible to have them lie on their faces for even short periods of time as respiratory difficulties are apt to develop. In the Children's Hospital School all patients in respirators are turned on each side for a definite period of time every day. At least once a day, the foot of the respirator is elevated to give the patient better drainage to the lower calyces. Before any of these changes of positions are made, the patient is given large quantities of water so that the dependent calyces may be better flushed out.

SUMMARY

Two patients were taken directly from the "iron lung" and successfully operated on for major urological conditions. A ureterotomy for calculi was performed on one; on the second, a ureterotomy for calculi and finally a nephrectomy. Both of these patients were anesthetized for 50 minutes. It would have been very difficult to perform these operations if the patients had not been in such an institution as the Children's Hospital School where there are respirators which can be taken directly to the operating room.

It is of interest that the 2 patients were adult sisters, that they developed the bulbar-spinal type of anterior poliomyelitis within 1 week and both were later operated on for stones in the urinary tract.

Chemical analysis of the stones removed from 1 patient showed just a trace of calcium. In those from the second, not even a trace was present. This indicates that in these 2 women decalcification of the bones and excessive calcium intake played no part in the development of the calculi. We believe that the immobilization itself with defective drainage of some or all of the calyces probably plays the most important role in the development of stones in recumbent patients.

The measures that are now routinely employed in the "iron lung" unit in the Children's Hospital School to prevent the development of calculi are outlined.

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METASTASES TO ENDOMETRIUM AND SKIN FROM CARCINOMA OF KIDNEY: REPORT OF CASE AND REVIEW OF LITERATURE

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The finding of metastases from carcinoma of the kidney, in extremely unusual sites, namely endometrium and skin, has prompted a presentation of the case report to follow. In a thorough review of the literature on malignant renal tumors, the only case of metastasis to the uterus from carcinoma of the kidney is cited in Willis' textbook *The Spread of Tumors in the Human Body*, and was reported by Eshner in 1908. Hinman and also Melicow, in personal communications, have no record of endometrial metastasis from renal tumor.

Reference to skin spread was found in only 8 cases. Cochez and Besser, in 1933, described a case of skin metastases from a papillary adenocarcinoma of the kidney. Melicow, in a comprehensive review of renal tumors at the Presbyterian Hospital, lists 5 cases of metastases to the superficial tissues, of which 3 were to the scalp, 1 to the scrotum, and 1 to the skin. Nalle recorded 2 instances of skin metastases from renal tumor.

CASE REPORT

R. A., a 65 year old female, was admitted to the Jewish General Hospital, March 15, 1946, with a history of painless hematuria of 3 months' duration. Past and familial histories were noncontributory. Physical examination revealed an elderly female, exhibiting moderate pallor, and evidence of recent weight loss. A ballottable mass was noted in the right loin. The blood pressure on admission was 140/90 mm. Hg.

The urine was light yellow and acid in reaction. The specific gravity was 1.016. There was a trace of albumin, sugar negative. Microscopic examination showed 6 to 8 red blood cells per high power field. The nonprotein nitrogen was 28.5 mg. per 100 cc. blood, and the creatinine was 1.3 mg. per 100 cc. blood. A chest x-ray was negative.

Cystoscopy was performed. The right pyelogram showed marked distortion of the renal pelvis, which suggested a tumor of the kidney. The left pyelogram was normal.

Exploration through the right loin revealed a large kidney with almost complete replacement of parenchyma by tumor. Firm adhesions bound the kidney to the inferior vena cava. Nephrectomy was performed with considerable difficulty, because of the close association of tumor to the inferior vena cava.

Pathological examination revealed adenocarcinoma of kidney, with invasion of renal capsule and capsular vessels (fig. 1, A). The mass of tumor was composed for the most part of rather complex tubular structures, which varied considerably in size and shape, many showing papillary infolding. These tubular structures were lined by single layers of relatively tall columnar epithelial cells, showing vacuolated cytoplasm and nuclei which varied in position, the majority being basally arranged. These nuclei were for the most part relatively uniform in size, shape and staining quality, although occasional variation was seen, and occasional mitotic figures encountered. Solid masses of granular tumor cells were also noted.

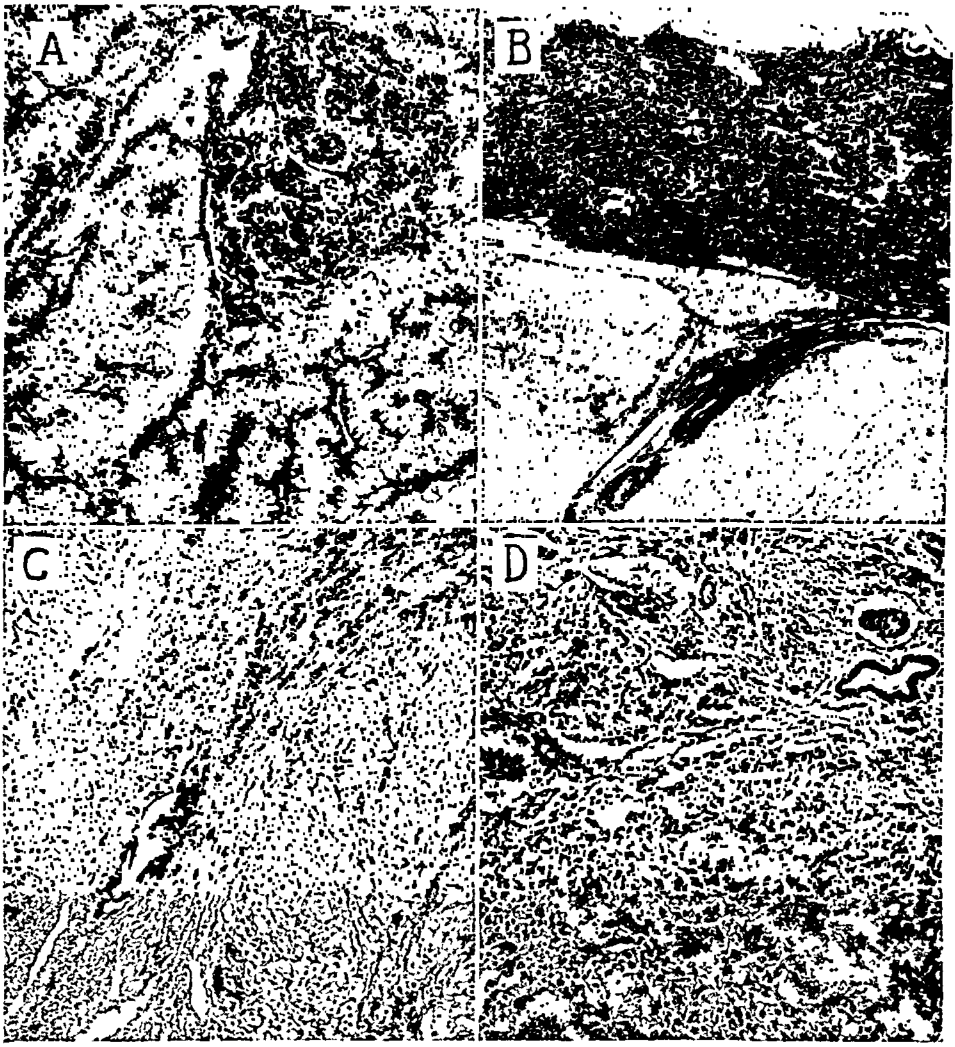

FIG. 1. *A*, Original adenocarcinoma of kidney, showing tubular structures lined by tall columnar epithelial cells. (× 95) Note also solid masses of distinctly granular cells. *B*, Skin biopsy, showing solid masses of metastatic tumor cells in subcutaneous fat. (Low power.) *C*, Endometrial curettings, showing metastatic tumor composed of large polygonal cells, with centrally placed nuclei. (× 95) *D*, Left uterine cornu (autopsy), showing typical tumor cells, with interstitial hemorrhage and necrosis. Note tumor cells in lymphatics of myometrium. (× 95)

The patient made a good recovery. She received a course of deep x-ray therapy over the operative site, and was discharged 30 days after admission.

She was readmitted to hospital 6 months later, October 1946, complaining of vaginal bleeding, of 2 months' duration. Physical examination revealed 2 circumscribed masses in the skin One was situated just to the left of the umbilicus, and measured 5 cm in diameter, the other in the right midaxillary line at the level of the seventh rib, measured 3 cm in diameter Both nodules were hard, fixed to the skin, nontender, and presented a superficial bluish discoloration, with dilated surface venules An x ray of the chest and long bones was negative for evidence of metastatic involvement Both skin lesions were completely excised, and a dilatation and curettage of uterus performed The patient made a good recovery following these biopsies, and was discharged from hospital 10 days later

Pathological examination confirmed the clinical impression of renal metastatic lesions in the skin Histological examination of skin biopsies (fig 1, *B*) showed them composed of tumor cells, with no acinar differentiation, and consisting of solid masses of tumor, in which the nuclei were relatively dense, and abundant though poorly defined granular cytoplasm noted Invasion of endothelial lined channels in some situations was noted

Histological examination of the endometrial curettings (fig 1, *C*) revealed sheets of tumor composed of large masses of tumor cells supported on delicate trabeculae The tumor consisted of fairly large polygonal cells showing relatively small, centrally placed nuclei, with one or more prominent nucleoli These nuclei varied only slightly in size and shape, but revealed occasional mitotic figures The tumor resembled a hypernephroid carcinoma of kidney

In December 1946, the patient complained of pain in the left thigh An x ray showed changes suggesting metastatic lesions in the lower portion of left femur Her general condition had deteriorated, she had become cachectic, with marked secondary anemia, and was admitted in extremis, January 1947 She expired 48 hours later

At autopsy, massive bilateral replacement of the adrenal glands by metastatic tumor was noted Examination of the lungs revealed no gross evidence of metastatic involvement, but histological study through several sections of lung tissue showed metastatic nodules replacing lung parenchyma Here the tumor was composed of irregular nests of cells, separated by thin bands of fibrous connective tissue The tumor cells were seen within blood vessels, and in alveoli

In the uterine cavity, one irregular dark brown, firm mass of blood clot, measuring 1 5 cm in diameter was intimately attached to the wall, in the region of the left cornu Sections through the hemorrhagic mass in the left cornu (fig 1, *D*) showed it to consist of a polypoid mass of typical tumor tissue, which was the seat of interstitial hemorrhage and necrosis The tumor invaded the myometrium for a short distance In this vicinity, masses of tumor tissue could be seen lying in thin walled blood vessels and lymphatics

Finally, metastatic lesions were demonstrated in the lower end of the left femur, and in the superior mediastinal lymph nodes

SUMMARY

A case of carcinoma of the kidney with metastases to the endometrium and skin has been presented It is interesting to note that these unusual sites of metastases were present in this patient, at a time when clinically demonstrable metastases were absent in the lungs and bones. However, it was only on histological examination of the lungs at autopsy, that microscopic foci of metastatic involvement were noted; and only toward the terminal phase of life that spread to the left femur became evident clinically.

In view of the extreme rarity of endometrial metastasis from renal tumor, and its association with another unusual site in the skin, this case was considered worthy of presentation.

The authors are indebted to Dr. H. C. Ballon, Department of Surgery; Dr. G. J. Strean, Department of Gynecology, and Dr. M. A. Simon, Department of Pathology, for their kind assistance in the preparation of this case.

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PYELITIS GLANDULARIS

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Pyelitis glandularis has been reported only 3 times (Paschkis, Brutt, and Foot) and is to be considered a medical rarity Ackerman and Plaut have each reported a case of mucinous adenocarcinoma of the renal pelvis, both kidneys also showing the presence of pyelitis glandularis Glandular development in the urinary vesical epithelium, resembling that of the intestinal tract, has been observed many times, both in exstrophy and anatomically normal bladders, and glandular epithelium in the ureter has been recorded once, by Paschkis

The rarity of pyelitis glandularis, the question of etiology, and possible consequences of such a lesion make its occurrence worthy of report

CASE REPORT

W K, No A28460, a 46 year old Negro, was seen in the Stanford Urological Clinic on September 17, 1945, complaining of an intermittent right flank pain of 2 weeks' duration Physical examination was essentially negative Laboratory studies Red blood cell count, 3 8 million per cubic mm , hemoglobin, 74 gm per cent, white blood cells, 8,000, blood urea, 24 mg per cent Urine loaded with leucocytes, albumin, 4 plus, cultures showed 2000 anaerobic non hemolytic streptococci per cubic centimeter Excretory urograms revealed a normal, well functioning left upper urinary tract, and a large staghorn calculus in the right kidney with only a faint trace of opaque solution in the calyces

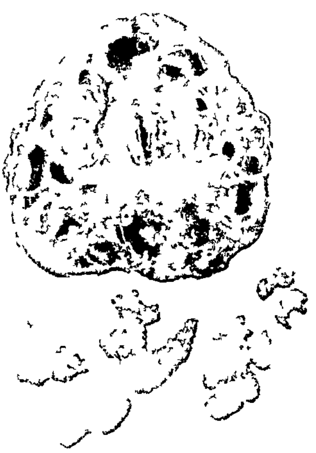

FIG 1 Abscessed kidney and calculus Note dark pelvic lining of lower pole

On September 24, 1945 a right nephrectomy was performed. There was only a moderate amount of perirenal fibrosis. He was discharged on October 12, 1945, and when last seen on November 24, 1945, his urine was clear and he was the feeling quite well.

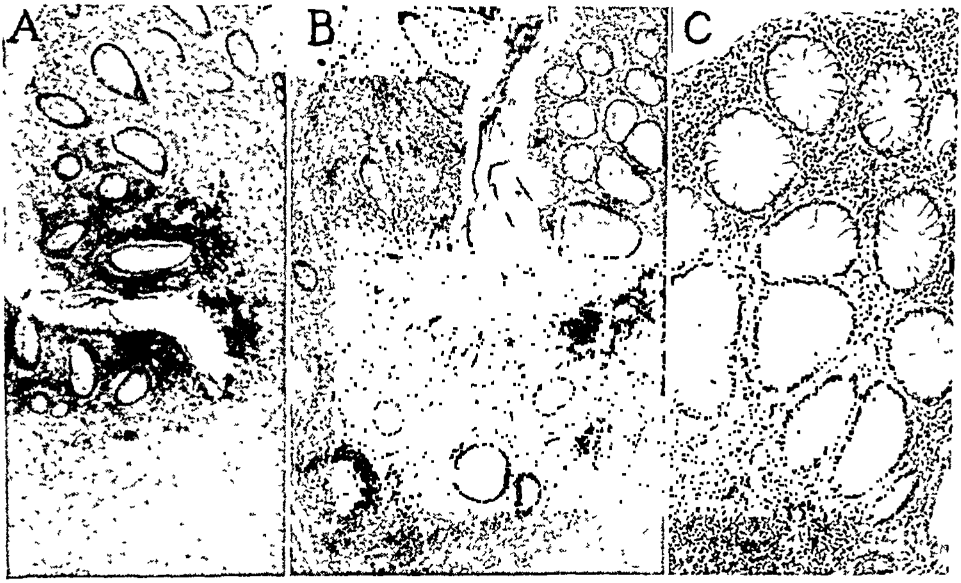

Fig. 2. *A*, Note papillary glandular lining and underlying smooth muscle. *B*, Loose stroma and numerous lymphocytes and lymph follicles surrounding glands. *C*, Well differentiated secreting glands and stroma infiltrated with lymphocytes.

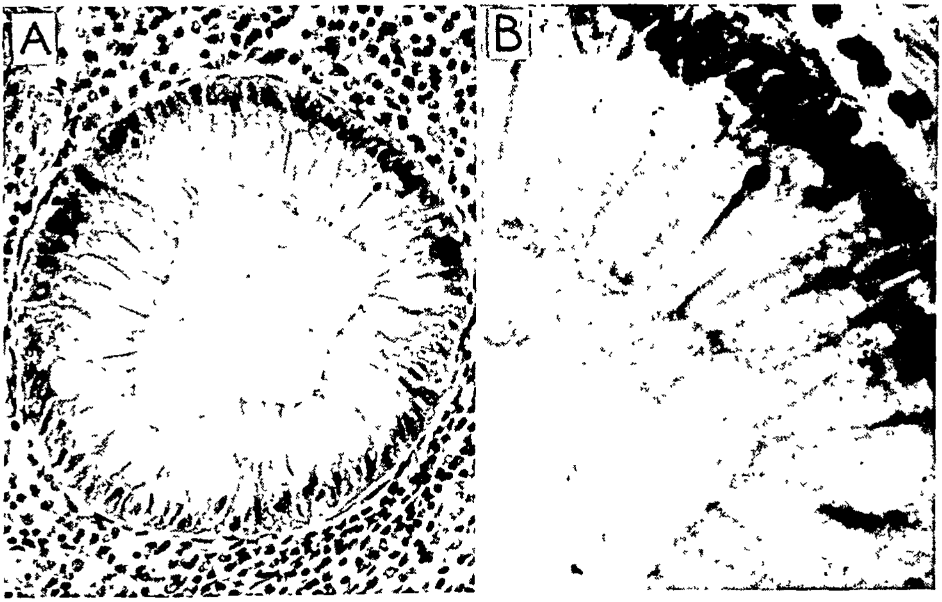

Fig. 3. *A*, Secreting goblet cells basal nuclei. *B*, Note globule of mucinous secretion, cuticular border and well differentiated basal nuclei.

The kidney measured 11.5 by 6 by 5 cm., and weighed 160 gm. It was practically destroyed by the large 55 gm. calculus and had numerous abscesses at the end of each ramification (fig. 1). The pelvis was granular, especially the lower pole which was red and thickened. The average thickness of the cortex was not more than 3 mm.

Histologically, the lining of the lower calyces and pelvis resembled the mucosa of the large bowel (fig. 2). The typical mucous glands were separated by abundant loose connective tissue heavily infiltrated by lymphocytes, and beneath the glands was a prominent layer of smooth muscle (fig. 2, *A* and *B*). In several places the pelvic lining had thrown itself into papillary projections (fig. 2, *A*). Lymph follicles with reaction centers were numerous (fig. 2, *B* and *C*). The glands had numerous goblet cells actively secreting mucin, and a thin cuticular border as seen in large bowel epithelium (fig. 3). The nuclei were basal in position and a definite basement membrane was present in each gland (figs. 3, *A* and 4 *A*). When the pathologist first saw these sections, the question was raised as to whether or not a section of the colon had been included in the nephrectomy. When assured that such was not the case, joint study and further sections showed this to be glandular pyelitis, complete in all respects to the glandular development of the intestinal type.

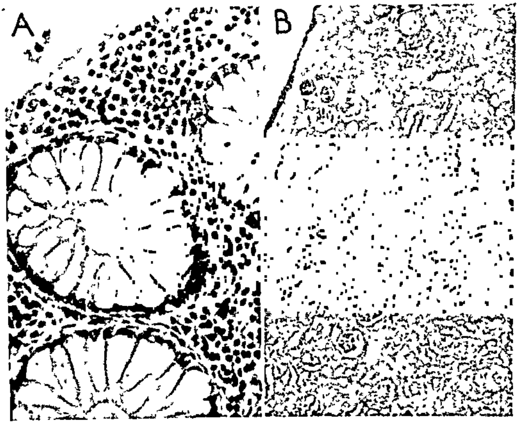

FIG. 4. *A*, Basement membrane present in each land. *B*, Sclerotic infected renal parenchyma.

Parenchymal sections showed glomerular fibrosis, dilated tubules lined by flattened epithelium and contining either hyaline casts or clumps of leucocytes. The capsule was thickened and there was marked infiltration by lymphocytes and polymorphonuclear leucocytes. Lymphoid follicles were numerous (fig. 4, *B*).

DISCUSSION

In the 3 reported cases of Paschkis, Brutt, and Foot, renal calculi were present, as in this case. Plaut's and Ackerman's cases of mucinous adenocarcinoma and glandular pyelitis also had calculi. Why chronic irritation results in the occurrence of glandular epithelium presents two plausible explanations; one, it is a metaplasia, or, pre-existing fetal cell rests have been stirred to activity.

Metaplasia can be seen in the same microscopic section in some cases of cystitis glandularis, showing the change from transitional, to columnar, and then to

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UNUSUAL URETEROGRAMS IN A CASE OF PERIARTERITIS NODOSA[1]

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Periarteritis nodosa or polyarteritis nodosa, as it is more accurately characterized, is a chronic systemic disease which has been found to involve the urinary tract in over 80 per cent of the reported cases.[3] The case reported herewith is of interest because of the extensive and unusual involvement of the ureters and the extraordinary and perhaps pathognomonic ureterograms associated with this localization of the inflammatory lesions.

CASE REPORT

Miss J. H., a 13 year old schoolgirl, was admitted to a suburban hospital on February 24, 1947 with acute abdominal pain and a rigid abdomen. The clinical picture, however, was not entirely typical of appendicitis and after several hours the acute abdominal symptoms subsided. Two days later she developed joint pain, migratory in nature, affecting the ankles, shoulders, elbows and wrists. These joint pains continued with varying severity for several weeks, but only on one occasion was there visible involvement of a joint, and this was swelling without redness of the left wrist. Four days after admission she developed a maculopapular rash on the extremities, most marked on the flexor aspects. By three weeks after admission the rash had disappeared but abdominal pain had developed in the right upper quadrant and she began to have chills with spiking temperature of 104 F. and other findings suggestive of sepsis. Penicillin and sulfadiazine were ineffective in controlling the fever and chills and the patient developed vomiting.

On March 25, an intravenous urogram showed excellent concentration, filling both pelves. The 60 minute film revealed considerable concentration of the dye remaining in both kidneys. The upper thirds of both ureters were markedly spastic, with moderate dilatation of the ureter (fig. 1).

The patient was seen by one of us (H. H. H.) on March 26. The abdomen was entirely negative except for some soft distension; the liver edge could be palpated below the costal border; there was no costovertebral angle tenderness. The urine sediment, other than showing 2+ albumin and 4 to 5 pus cells in each high power field, was negative. The nonprotein nitrogen was 32. Because of the negative physical and laboratory findings, a complete urological investigation was not made.

On March 30 she was seen again because of a sudden onset of right upper quadrant pain. Her abdomen was considerably distended at this time, and most of the tenderness, with some spasm, was over her gallbladder region. The white count was 17,000; her temperature was 100 F. and it was believed that she had a surgical abdomen, not involving the renal tract. That same afternoon an exploratory laparotomy was done through a right upper quadrant muscle-splitting incision. The liver was enlarged and the capsule showed numerous linear, grayish-white streaks, arranged in a spider-web fashion. There was considerable engorgement and hyperemia of the liver. Aspiration cultures were taken and later reported to show no growth. A routine appendectomy was done. The intestine showed no focal lesions, nor was there any demonstrable lymphadenopathy in the mesentery.

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[1] Read at annual meeting, North Central Section, American Urological Association, Cleveland, O., October 24, 1947.

[2] Research Fellow in Legal Medicine, Harvard Medical School.

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The postoperative course was progressively downhill, with exacerbated vomiting, unrelieved by Wangensteen decompression.

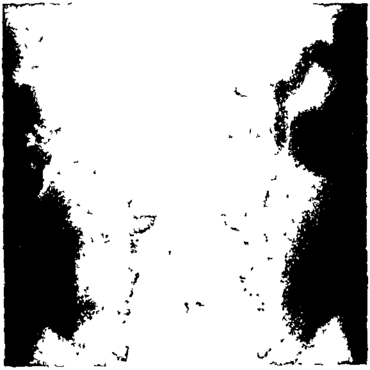

FIG. 1. Upper thirds of both ureters are markedly spastic with moderate dilatation, indicating some degree of obstruction due to marked irritability in proximal third of ureters. Sixty minute film shows considerable concentration of dye within both kidneys and both ureters.

On April 4, a second intravenous pyelogram showed the same deformity in the ureters that was found on March 25, and the pelves still contained a considerable amount of dye at the end of 1 hour.

On April 10, the patient developed distention of the abdomen and marked oliguria; the nonprotein nitrogen was reported as 160 mg. per cent and in the last 12 hours preceding death she developed generalized convulsions. She expired on her forty-sixth hospital day.

During the hospital stay, the sedimentation rate had increased from 40 mm. per hour on admission to 140 mm. per hour prior to laparotomy. There was a marked anemia with a red blood count around 2,000,000 and a hemoglobin of 10 per cent. The white blood count varied from 9,000 on admission to 17,000 prior to laparotomy.

The pathological report on the appendix (Dr. Olga Leary) showed "an endarteritis and inflammatory exudative process involving the arterioles." Electrocardiograms during the hospital stay were not abnormal.

The final clinical diagnosis, made as a result of the laparotomy, was periarteritis nodosa with terminal nephritis and uremia.

Autopsy: The examination was performed by one of us (R. S. F.) 6 hours after the patient expired. The significant macroscopic findings were confined to the urinary and intestinal tracts.

The kidneys weighed a total of 300 gm. The capsules stripped readily, exposing brownish-yellow tissue with numerous bright red hemorrhagic areas, varying up to 5 mm. in diameter. On section, there was marked vascular congestion with numerous hemorrhagic foci similar to those seen on the surface throughout the cortex and medullary zones (fig. 2). Throughout the kidneys, especially at the cortico-medullary junction, there were numerous white glistening structures which, on section, showed tiny lumina and were recognized as small blood vessels with thickened walls. The parenchyma between the hemorrhagic foci was yellowish-brown. The entire kidney was soft and flabby. The renal pelves were injected, but grossly free of exudate.

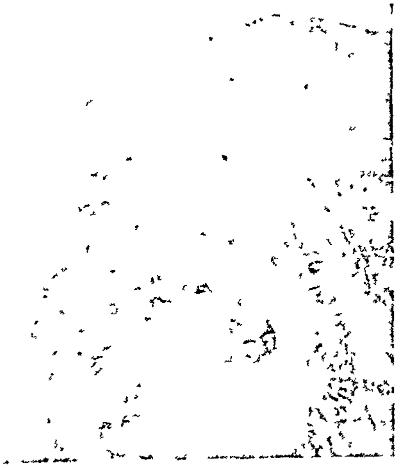

FIG. 2. Photograph of cut surface of upper pole of kidney, showing enormously swollen cortex which is traversed by radial columns of hemorrhage and stippled by petechiae.

The ureters were not dilated, but the walls, especially throughout the upper half of each ureter, were markedly thickened and of a glistening, pearly-gray, edematous character. Lying medial and parallel to the left ureter for a distance of 3.5 cm., beginning approximately 2.5 cm. below the ureteropelvic junction, there was a conglomerate group of lymph nodes, the largest of which measured 2.5 cm. in length. These were of a soft cellular, nonhemorrhagic character and resembled the lymph nodes seen elsewhere in the abdomen. This mass of lymph nodes impinged upon the left ureter and compressed it to some degree. There was hyperemia of the bladder mucosa.

The esophagus was unremarkable. The stomach contained about 100 cc of liquid "coffee ground" material. The jejunum and proximal ileum were markedly distended and, especially in the ileal segment, the serosa was intensely injected and overlaid by a small amount of fibrinous exudate. The distention terminated abruptly, approximately 3 feet above the ileocecal valve and the distal portion of ileum was collapsed and bound down by organizing fibrinous adhesions which apparently caused nearly complete obstruction. The adhesions were readily stripped, however, and the intestinal wall in this segment was only slightly thickened and was not hemorrhagic. The mesentery of the small bowel showed moderate dilatation of the blood vessels. At the root of the mesentery there were numerous enlarged lymph nodes varying up to 15 mm. in diameter. The appendical stump was well healed.

Microscopic. Active vascular lesions were confined to the kidneys, ureters and gallbladder. In these situations many of the medium and small arteries and the arterioles were involved by a severe inflammatory and proliferative process (fig. 3). The vessels affected ranged from about 20 micra to 2 mm. in diameter and where several adjacent vessels were affected there was coalescence of perivascular zones of inflammation to form nodules up to 5 mm. in diameter. The involvement of larger arteries was segmental, and there were occasional areas where one side of the wall was markedly thickened and infiltrated, while the opposite wall was normal in thickness, and showed an orderly arrangement of its various layers. The lesions varied in age from early acute inflammation, with cellular exudation, to "the healing stages," characterized by marked proliferation. In the acute inflammatory stage (fig. 4, A) the intima and the inner media were converted into an eosinophilic granular or hyaline substance, and the outer media and adventitia were intensely edematous, with wide spaces between swollen, pale staining muscular fibers. The entire thickness of the wall and an adjacent zone frequently as wide as the vessel itself, was infiltrated with neutrophils, lymphocytes, plasma cells and occasional eosinophiles. In many of the smaller vessels

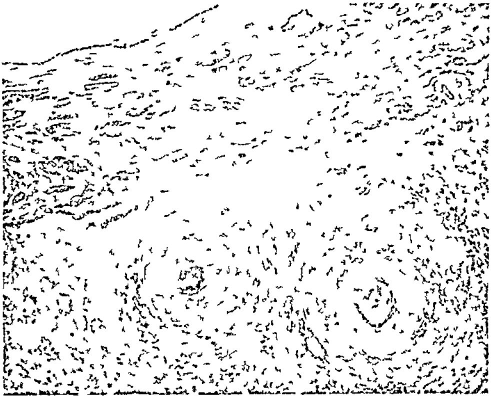

Fig. 3. Photomicrograph showing involvement of adjacent vessels, one, acute inflammatory stage, the other, healing. Ureteral lumen is at upper left. × 12

the lumina were occluded by fibrinous thrombi and cellular exudate. In the lesions of longer duration (fig. 4, *B*) the intramural cellular exudate was less prominent, and there was marked proliferation of fibroblastic elements with thickening of the intima to two or three times the narrowed diameter of the lumen and similar two- or three-fold proliferative thickening of the muscularis and adventitia. In these the adventitia usually contained many lymphocytes and other chronic inflammatory cells. The proliferating fibrous elements in the intima and media were in general concentrically disposed, but showed frequent whorl formation and other irregularities. The elastic lamellae caught in whorls were sometimes reduplicated or split into as many as five distinct and discontinuous layers. At this stage the granulomatous character of the inflammation was best seen, and the fibrosis involving adjacent vessels often became confluent.

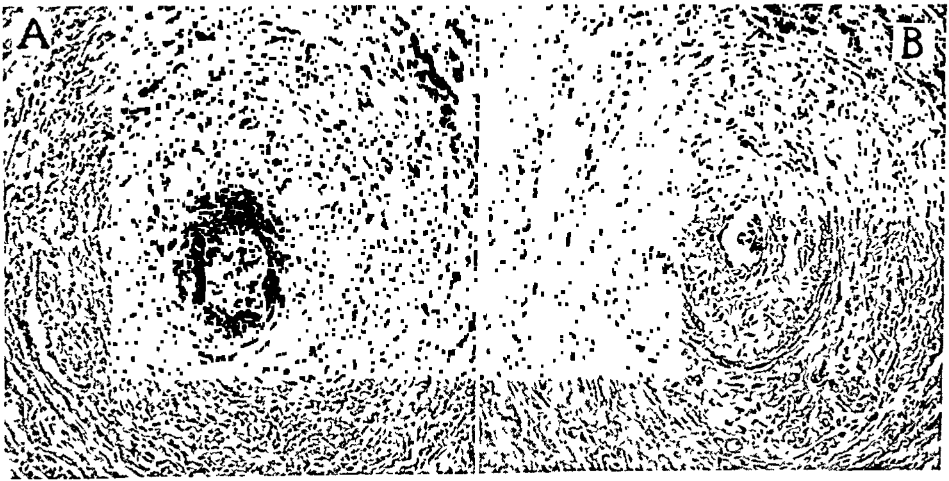

FIG. 4. *A*, Higher magnification of figure 3. Showing acute stage of inflammation. Note necrosis of intima and thrombus in lumen and cellular exudate in media and adventia. × 160. *B*, Higher magnification of figure 3. Showing healing vessel. Note markedly thickened intima and narrow but patent lumen. Very little cellular exudate remains. × 160.

Occasional vessels were densely scarred and inflammatory cells were absent. There was sometimes recanalization of occluding thrombi and healing was complete. Other vessels were represented by contracting scars with complete obliteration of structure. In occasional vessels the inflammation seemed limited to the adventitia and periarterial tissue. Veins were involved only when close to inflamed arteries. Aneurysmal dilatation of affected vessels was not seen.

The renal parenchyma was widely involved by the inflammatory process. In the uninvolved areas there were groups of markedly dilated and engorged capillaries, suggesting dilatation to maintain blood flow through collateral shunts and to compensate for thrombosed vessels. There was marked cellularity of the glomerular capillaries with swelling of the basement membranes. Cloudy swelling of cortical tubules was moderate.

The ureteral epithelium was edematous and there was much desquamation into the lumen. The most severe reaction in the entire urinary tract was the panarteritis and arteriolitis distributed throughout the circular muscular wall, and especially in the adventitial connective tissue of the ureters (figs 3 and 4) In the bladder an occasional vessel was involved by the periarteritis, but the muscular wall was otherwise normal The mucosa was somewhat thickened and edematous, and in the deeper layers there was conspicuous polymorphonuclear infiltration The lymph nodes in the region of the left ureter were characterized by marked hyperplasia of the reticulum and widespread active and healing arteritis

Sections of the gallbladder and the cystic duct, artery and lymph node showed marked edema and multiple acute and healing arterial and arteriolar lesions The lungs, liver, heart and mesenteric nodes contained occasional vessels the seat of "healed polyarteritis"

The anatomical diagnoses were periarteritis nodosa with extensive involvement of kidneys and ureters, intestinal obstruction, recent appendectomy Death was attributed to periarteritis nodosa of the urinary tract with terminal uremia and was probably contributed to by intestinal obstruction

DISCUSSION

As in the majority of previously reported cases the initial signs and symptoms of the disease in this patient were difficult to evaluate Boyd[4] and more recently Diaz-Rivera and Miller[5] have commented on the bizarre abdominal pain accompanying polyarteritis nodosa In this patient, the combination of abdominal pain, spasm and tenderness with spiking fever led to exploratory laparotomy and the diagnosis was established by pathological examination of an incidentally removed appendix

Despite the frequent involvement of the kidney in polyarteritis nodosa we have not found descriptions of ureteral lesions such as were present in this case Contratto[6] has recently reported the case of a Chinese who died of periarteritis nodosa with renal impairment, acute hypertension and a large perirenal hematoma Five months before death "intravenous pyelograms and genito urinary studies revealed no abnormalities" In the past 12 years 10 of 14 cases of periarteritis subjected to autopsy at the Mallory Institute of Pathology showed renal involvement, and in 2 of these ureteral lesions were present In 8 cases the ureters were not described in the autopsy protocols Only 1 of the 14 had a complete antemortem urological investigation and the ureters were reported as normal

A diligent search of the literature has failed to reveal ureterograms such as were found in this case The unusual picture (fig 1) of moderate dilatation with marked spasticity of the upper third of both ureters was present in 2 ureterograms obtained at a 10 day interval and served to focus attention on the urinary tract involvement. The postmortem demonstration of extensive ureteral polyarteritis with co-existing acute inflammatory and proliferative stages of the arterial lesions indicates a considerable duration of the disease process in the ureters.

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SUMMARY AND CONCLUSIONS

A case of periarteritis nodosa with extensive ureteral involvement is reported. The ureterograms show changes not found in other pathological conditions.

In view of the findings in this patient and the reported fact that 80 per cent of periarteritis nodosa cases show evidence of urinary tract involvement, it appears that urological examination of patients having bizarre abdominal pain possibly due to periarteritis nodosa should be a routine preoperative procedure.

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SUPERNUMERARY KIDNEY WITH ABERRANT URETER TERMINATING EXTERNALLY

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Supernumerary kidney has been reported previously in only 45 cases Aberrant termination of ureters has been reported more often The combination of a supernumerary kidney with termination of its ureter in the vaginal vestibule has not been previously reported This report therefore deals with the rarest congenital renal anomaly in conjunction with another quite rare congenital urinary tract anomaly

Embryologically the kidney develops from an anlage called the mesochyme or renoblast The ureter develops from the caudal segment of the wolffian duct and grows cranially Usually these two structures fuse, resulting in the normal kidney and ureter Deviation from the normal developmental processes results in congenital anomalies and the rarest of these is supernumerary kidney It is differentiated from double or fused kidneys by the fact that the accessory, third kidney is a distinct, encapsulated, parenchymatous mass either completely unrelated to the other kidney on the same side or at most attached to it with loose cellular tissue It has its own blood supply and separate ureter The ureter frequently joins the other ureter on the same side or enters the bladder separately Rarely does it terminate outside the urinary tract

Anomalies of the urinary tract frequently remain silent but they do predispose to pathologic lesions which in turn manifest themselves clinically Most of the cases of supernumerary kidney were diagnosed at surgery, only 6 by pyelography and a few were discovered on routine autopsies The accessory kidney is more often below and usually smaller than its companion Its incidence is the same in both sexes but occurs more often on the left side. The symptoms presented depend on the disturbance of function of the accessory organ or on the disease present in this organ Occasionally contiguous organs are disturbed in their function When the ureter drains into the vagina, vestibule or distal portion of the urethra, the patient has constant urinary drainage in addition to normal voiding The diseases encountered include urinary calculi, pyonephrosis, hydronephrosis, renal ptosis, and pyelonephritis This third organ is especially prone to develop urinary stasis and infection, particularly when there is inadequate ureteral drainage

The symptoms can include any of the following: pain, fever, palpable tumor, hematuria, dysuria or even gastro intestinal dysfunction The treatment usually requires removal of the accessory organ Occasionally the companion kidney requires removal and the accessory kidney may be left in place to function normally The anatomic and physiologic aberrations are practically as numerous as there are cases reported Obviously there is therefore no standard description for this congenital anomaly

The case here reported is the forty-sixth supernumerary kidney thus far recorded in medical literature and is the first one in which the ureter terminated in the vestibule of the vagina.

CASE REPORT

Mrs. J. R. (No. A-21938) was first seen in 1943, aged 23. Her complaint was urinary leakage all her life even though she had normal urination. She had the usual childhood illnesses. Her parents scolded her and even beat her frequently because of her incontinence. Her playmates also knew of her affliction and made life miserable for her. She therefore developed an inferiority complex which reflected in her personality and conduct. At the age of 18 she married a childhood acquaintance from whom she concealed her physical defect for 3 years. During this 3 year period she had 2 uneventful pregnancies. When her husband finally learned of her physical defect he was fortunately sympathetic, which made life more tolerable for her. Later she learned that there might be a cure for her so she sought medical aid.

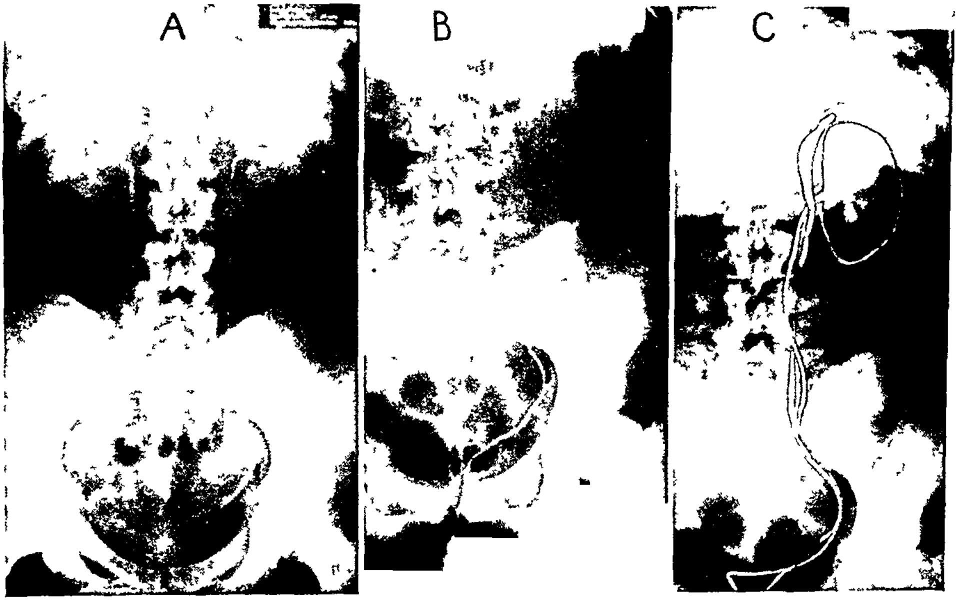

Fig. 1. *A*, Intravenous pyelogram. *B*, Injection of aberrant ureter to outline ureter and third kidney. *C*. Retrograde pyelogram, showing normal left kidney and supernumerary kidney and aberrant ureter (with superimposed tracing).

Examination showed no abnormalities. Intravenous urograms (fig. 1, *A*) showed normal outline, position and function of the upper and lower urinary tract. Cystoscopic examination showed a normal bladder with the 2 ureteral orifices normally situated and functioning well. Close inspection of the vaginal vestibule revealed an area of moisture midway between the urethral meatus and the anterior border of the vaginal orifice. By probing a slit was located in the mucosa, just to the left of the midline, and which could be probed for a distance of 1 cm. Urine was seen escaping at this point. The sinus did not admit a ureteral catheter but a blunt needle was introduced for 1 cm and diodrast injected. X-ray (fig 1, *B*) showed the diodrast outlining an aberrant ureter that led to a supernumerary kidney just above the normal left kidney. The ureter crossed its mate at the ureteropelvic junction of the companion kidney, thereby being a mechanical hazard to the normal kidney (fig 1, *C*).

Discovery of this reason for her life long incontinence was a boon to her morale. Now she finally learned that her abnormality was not of her own making and, more important, it could be corrected The various possibilities of treatment were evaluated. The injection of a sclerosing solution through the ureter into the third kidney was dismissed as being hazardous and not likely to render the kidney nonfunctioning Ligation of the ureter through the anterior vaginal wall could have been accomplished easily It was not chosen because of the chance of pyelonephritis in the obstructed third kidney and also the likelihood of the dilated aberrant ureter compressing the ureteropelvic junction of the normal kidney The remaining and proper procedure was removal of the extra kidney and the upper portion of its ureter.

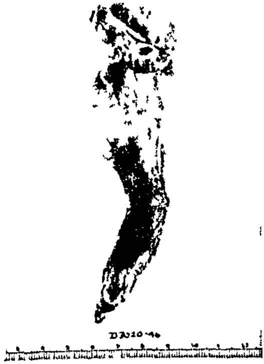

FIG 2 Sectioned specimen, showing kidney and upper portion of ureter

The patient waited 3 years before submitting to surgery in August 1946, at which time she was 26 A high exposure was obtained by making the incision over the twelfth rib and removing the rib There was a normal left kidney and ureter In addition there was a small kidney just above the normal kidney This smaller organ had its independent artery and vein and its ureter coursed downward anterior to the other ureter but posterior to the vessels of the companion kidney The ureter was clamped, cut and ligated at an eleven centimeter level and dissected upward to liberate it from the ureteropelvic junction of the other kidney The vascular pedicle was then clamped, cut and ligated and the accessory kidney dissected from its attachment to the normal kidney and removed with 11 cm. length of its ureter. The wound was closed in the usual manner and drained with a Penrose drain.

She has felt entirely well since surgery. Removing her lifelong affliction has changed her from a shy girl with an obvious inferiority complex to a cheerful, ambitious, sociable wife, mother and member of society.

The surgical specimen (fig. 2) consisted of a hypoplastic kidney weighing 9½ gm., and having attached 11 cm. of dilated ureter. The kidney measured 3.3 by 2 by 0.5 cm. in maximum diameters. The renal parenchyma was of varying thickness and a distinct corticomedullary junction was seen. The calyces were dilated. The ureter had a uniform circumference of 2 cm. Microscopic examination of the kidney showed the glomeruli fairly numerous and of normal cellular makeup. There was a marked collection of hyalin casts in the tubules. Diagnosis was hypoplastic supernumerary kidney with chronic pyelonephritis and a hydroureter.

SUMMARY

Supernumerary kidney is the rarest renal anomaly. Aberrant ureter is a quite rare urinary tract anomaly. The combination of a third kidney with its ureter ending in the vaginal vestibule has not previously been reported.

The embryologic basis for such a congenital maldevelopment is given.

The definition of supernumerary kidney and its differentiation from double or fused kidneys is outlined.

A complete survey of all the previously reported cases shows that this renal anomaly occurs more often on the left side, is more often below the companion kidney, and its incidence is the same in both sexes. It gives symptoms only when its physiology is disturbed or when disease develops in the anomalous kidney or ureter. The various pathologic possibilities and resulting clinical manifestations are enumerated.

The diagnostic procedures are outlined and various methods of treatment evaluated.

The author's case is reported, this being the forty-sixth case known to be recorded at the present time.

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PRIMARY BENIGN NEOPLASM OF THE URETER

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It is the object of this report to record a case of benign primary neoplasm of the ureter and to review the English literature on the subject of benign primary ureteral neoplasms. The rarity of this type of neoplasm is shown by the fact that Renner in reviewing 130,000 autopsies at the Vienna Pathological Institute in 1931 found only 3 examples of ureteral tumors.

The first report of benign neoplasm of the ureter was given by Lebert in 1861, a polypoid fibroma, according to the pathologic report. Lancereaux reported a second in 1865, a papilloma of the ureter. Extensive reviews of the literature have been made by Melicow and Findlay in 1932, and by Rusche and Bacon in 1938. The report of Melicow and Findlay included a total of 28 cases from the literature, however, in view of the fact that 12 of those cases had no histologic study, it was felt that they should not be considered as valid case reports in tabulating a total. The review of Rusche and Bacon in 1938 included in a total of 11 cases, 2 granulomata which were not true neoplasms, and a third case which was apparently not benign in view of the statement. "Islets of epithelial cells were noted in lymphatic channels in the submucosal tissue", thus 24 incidences of benign ureteral neoplasm have been published through 1938.

An unusual neoplasm was a cavernous hemangioma which encircled the ureter and was adherent to the adventitia in several places but had not constricted the ureter or produced any obstruction. Ewing cites a pure myoma of the ureter, reported by Buttner. A neurofibroma was reported, apparently arising from the ureter and encircling it. An unusual finding was that of an endometrioma of the ureter, intraureteral, which, however, showed no cyclic bleeding and apparently was not functioning as true endometrial tissue. The author pointed out that the cyclic occurrence of intensified symptoms, especially hematuria in a female, should always raise the suspicion of a ureteral endometrioma.

A report of 1944 brought out a total of 27 cases of benign ureteral neoplasms in which the diagnosis was verified by 1) inspection of the interior of the renal pelvis and entire ureter and 2) microscopic examination of the tumor. Sixteen other reported cases were rejected by the author because they failed to satisfy one or both of these criteria.

Reports of benign ureteral neoplasms in recent years have all been confirmed by microscopic studies.

CASE REPORT

A married, 60 year old white man complained of hematuria of 3 years' duration. The present illness began 3 years previously with an attack of painless hematuria lasting a few days. The second attack occurred 1 year later with a week's duration of bleeding. Intravenous pyelogram at that time demonstrated no disease. From that time, until shortly before his visit to my office, he had mild attacks of hematuria at intervals of about 6 months. The last attack was 1 week previously with hematuria lasting about 4 days, followed by cystoscopy and pyelogram at a hospital by another physician but results were inconclusive. Occasional frequency and nocturia were present off and on. The stream was normal. There was no loss of weight elicited. He complained of some dull pain in right lower quadrant. The family and past histories were essentially negative.

Physical examination disclosed no significant abnormality. The blood pressure was 140/85. Urinalysis showed nothing abnormal, but the urinary sediment contained a few pus cells and 8 to 10 red blood cells. The prostatic secretion was normal.

A diagnosis of probable tumor of the genito-urinary tract was made. While making arrangements for cystoscopy and pyelography, the patient had another attack of severe bleeding, felt faint, and had recurrent pain in the left lower quadrant and flank 1 week after examination.

Six days later examination with a No. 24 McCarthy cysto-urethroscope was negative. Indigo carmine returned from both sides in good concentration in 6 minutes. Because of previous x-rays and cystoscopy elsewhere, add the normal function from the right kidney by indigo carmine, the right orifice was not catheterized. The left ureteral orifice was catheterized with a No. 10 Woodruff terminal eye catheter, and a uretero-pyelogram was performed with 20 per cent diodrast solution. The ureter filled only about one-half its length, and no dye would go above it into the kidney. Because of this, the Woodruff catheter was removed and a No. 5 x-ray catheter was passed to the renal pelvis which filled with dye and then a ureteropyelogram taken. There was a large filling defect in the ureter about 2 cm. in diameter opposite the fourth lumbar vertebra (fig. 1). The patient left the table in good condition.

After the retrograde pyelogram was taken a diagnosis of primary tumor of the ureter was made, and hospitalization advised. Complete laboratory studies were carried out before the operation. Urinalysis showed urine to be straw-colored, slightly turbid, pH 4.5, specific gravity 1.015, slight trace of albumin, no sugar or acetone, 2–4 white blood cells per high power field, 1–3 red blood cells with occasional renal cells seen to high power field. Urine culture negative. Red blood count 4,700,000; hemoglobin 92 per cent. White blood count: 5,400, polymorphonuclears 58 per cent, lymphocytes 40 per cent, eosinophiles 2 per cent. Smear normal. Blood chemistry: nonprotein nitrogen 44 mg. per 100 cc of blood, sugar 85 mg. per 100 cc of blood, prothrombin time normal, Hinton negative, blood type B, Rh positive.

On May 1, 1946, four days after admission, a left nephroureterectomy was performed under spinal anesthesia. An incision was made over the left loin parallel to the twelfth rib, about 7 inches in length. This was carried through the skin, fascia and muscles. The perirenal space was opened, and the kidney delivered. The ureter was freed downward for a considerable length where it widened perceptibly, dilating to about 3 cm. in diameter at the site of the tumor.

The latter was found about 7 cm. from the ureterovesical junction. At the site of the tumor there were numerous telangiectatic vessels coursing over the ureter surrounding the tumor. The tumor could be felt as a firm, flat, mobile mass in the ureter. Below it the ureter resumed its normal caliber. The incision of the loin was enlarged anteriorly and the ureter was dissected down almost to the bladder. At this point two large clamps were placed on the renal pedicle and the kidney was cut away. The pedicle was tied with a circular tie of No. 2 double chromic catgut, and a transfixation suture of the same material was placed between the 2 clamps. The kidney and ureter were then held in 1 piece and stripped down as low as possible at the site of the normal ureter low down near the bladder. Two clamps were placed on it and it was cut off between the clamps. A tie of No. 1 chromic catgut was placed around the stump of the ureter, the latter carbolized and allowed to recede. A Penrose drain was placed at the stump of the ureter, another in the renal fossa, and the wound sutured in layers with No. 1 chromic catgut. Black silk, interrupted, was used for the skin. Patient stood operation well; no shock or hemorrhage.

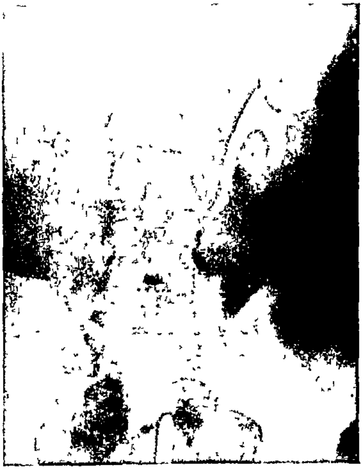

FIG. 1 Ureteropyelogram. Note filling defect in ureter (left)

The patient made an uneventful recovery. The patient was out of bed on the second postoperative day; the drains were removed on the seventh day, and sutures on the ninth day. The patient was discharged on the tenth day.

After discharge the patient continued to have a serous discharge from the drain site for a few weeks, the latter then healing completely. Subsequent examinations demonstrated a solid scar with no hernia. The patient returned to work 2 months after the operation. Urinalysis repeatedly since then has been negative chemically and microscopically. Fifteen months since the operation, there has been no recurrence of hematuria and the patient is working and well.

PATHOLOGY

The specimen consisted of a left kidney with attached ureter, the kidney measuring 10 by 5 by 2.5 cm. and the ureter 10 cm. in length and 0.7 cm. in circumference in its first 7 cm. (fig. 2, *A*). Beyond this point the circumference widened to 2.8 cm. and narrowed to 1.7 cm. at the distal resected margin. The kidney weighed 115 gm. The surface of the kidney was smooth and brown pink. The cortex was well delineated and measured 0.6 cm. in width. The calyces and pelvis were slightly dilated. The mucosa of the pelvis presented a few pin point petechial hemorrhages but was otherwise smooth, glistening and not thickened. The proximal 7 cm. of the ureter revealed 2 small, focal areas of hemorrhage just beneath the pelvis. Otherwise the mucosa was smooth and not thickened. At a point 7 cm. from the origin of the ureter, and projecting into the lumen, was a papilliferous structure which measured 2 by 1.4 by 0.8 cm., and was attached by a slender pedicle to the mucosa. This pedicle measured 1.1 cm. in length and 0.2 cm. in diameter. The polypoid structure was pink and moist, freely movable, and of doughy consistence (fig. 2, *B*). The remainder of the ureter was dilated and was thinned out and smooth in the region where it surrounded the polyp. There was no gross evidence of a recent or healed inflammatory process in any portion of

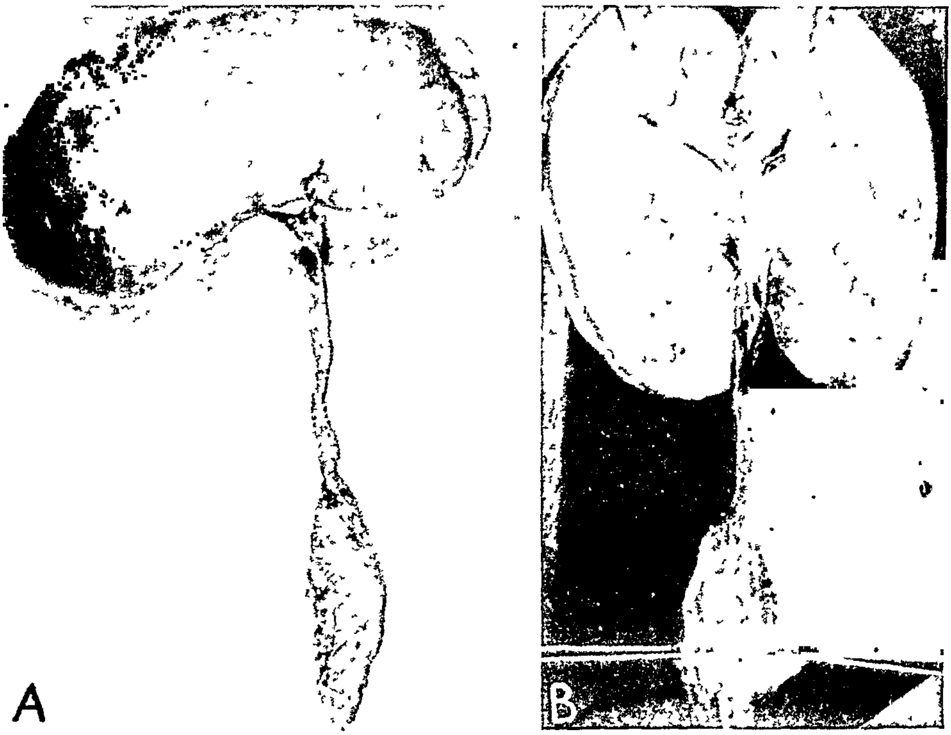

FIG. 2. *A*, Kidney and ureter. Note dilatation and distortion of lower ureter. *B*, Kidney and ureter opened, to demonstrate papilloma of ureter.

the ureter. The distal 2 cm. of the ureter presented a corrugated gray mucosa. The gross diagnosis was *papilloma of the ureter; minimal dilation of pelvis and calyces of kidney.*

Microscopic examination of sections from the kidney: The overall pattern was normal, with a cortex of normal width and containing a normal number of glomeruli. All the tubules of the kidney were slightly dilated. The capsule was not thickened and there was no evidence of an inflammatory process in the kidney. The glomeruli revealed slight but definite increase in thickening of the parietal layer of Bowman's capsule; the basement membrane of the tuft capillaries was swollen, focally, and thickened by a translucent, pale, pink substance. Arterioles showed no significant reduction in lumen width; the walls were minimally thickened.

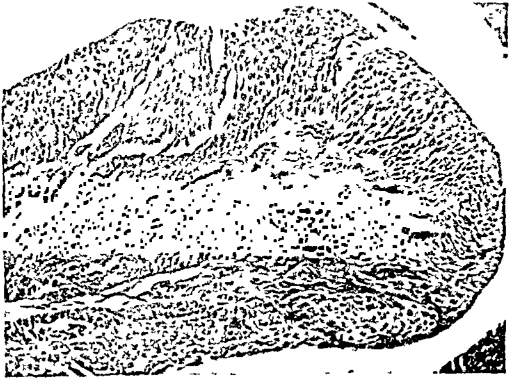

FIG. 3 Papilloma of ureter. Note transitional cell pattern, palisade arrangement, and intact basement membrane. × 100, Microphotograph.

Ureteral tumor: The histological sections demonstrated clearly the delicate papillary nature of the tumor. It was composed of a core of vascularized connective tissue with branching processes of transitional epithelium (fig. 3). Depending upon the plane in which the section was cut, the epithelium had the form of elongated cells or polyhedral cells. There was a distinct basement membrane in all processes of the tumor and the line of junction between epithelium and connective tissue stalk was sharp. The cells of the tumor proper were of approximately the same size and shape, being polyhedral in outline with pink cytoplasm. They had an oval or round nucleus in which the chromatin was finely dispersed at the periphery of the nucleus. Some nuclei contained small, acidophilic nucleoli. A rare mitotic figure was seen. Hyperchromatic nuclei were not noted and there was no invasion of the stalk in the sections examined.

Ureter: Sections taken at various levels above and below the tumor revealed a mucosa of normal transitional epithelium. The wall, however, above the tumor, was thickened due to an hypertrophy of the musculature. Diagnosis: Papilloma of ureter, transitional cell type; no evidence of malignancy; minimal hydronephrosis and slight hypertrophy of ureteral wall.

DISCUSSION

It has been stressed by numerous observers that the outstanding symptoms are pain, hematuria and a palpably enlarged kidney. The pain may be severe and of the quality of colic due to the passage of clots of blood; this pain may also be referred to the groin, scrotum and penis. Another type of pain, dull and aching, may be felt in the flank; this is due to the hydronephrosis; or a dragging sensation may be experienced by the patient because of the hydronephrosis. In some instances a palpably enlarged kidney may be present due to the obstruction and if a superimposed infection occurs the clinical picture may be that of a renal bacterial infection or even sepsis.

Hematuria, profuse, spontaneous and intermittent, gross or microscopic, was noted in about 70 to 75 per cent of the cases. This is both the most prominent and earliest symptom. The finding of an enlarged and palpable kidney was reported in 40 per cent of cases, almost always due to hydronephrosis. The tumor itself is rarely palpable. Urinary frequency has been noted, more marked in tumors in the lower third of the ureter. A persistence or recurrence of hematuria after nephrectomy for hydronephrosis has been noted and then the real diagnosis of ureteral neoplasm has been made.

As pointed out above, the cyclic occurrence of intensified symptoms especially hematuria in a female should bring to mind the possibility of endometrioma of the ureter. A rather unusual situation was encountered in the report of a pulsating cavernous hemangioma of the ureter simulating an inoperable carcinoma of the bladder. The angioma of the ureter made its impression beneath the mucous membrane of the bladder in two places, eroding it with the production of hemorrhage, so that it gave every appearance of a vesical growth.

The diagnosis of ureteral neoplasms depends upon history and physical examination, cystoscopic findings, and x-ray examination. Cystoscopic examination may reveal pouting at the ureterovesical orifice or the tumor may actually protrude through and be visualized directly. Dilatation and injection of the ureteral orifice on cystoscopy are suggestive of the possibility of ureteral disease and call for further investigation with the object of ruling in or out the presence of neoplasm. The passage of a ureteral catheter and meeting obstruction is very suggestive. Further attempts with the passage of blood is also suggestive of the possibility of ureteral tumor. Other diagnostic procedures are the intravenous phthaleïn test, as a differential for the 2 ureters. A most important procedure is the ureterogram. Conditions to be differentiated in ureterograms are malignancy, tuberculosis, inflammatory strictures and calculi.

The treatment of ureteral neoplasm has been total ureteronephrectomy, particularly since papilloma is found more commonly than the other rarer conditions and because of the potential malignancy of benign transitional cell neoplasms. The operation has been that of Beer who states that the added risk of removing the whole ureter through the second pararectus incision is negligible.

It has been recommended that an ounce of 1:20,000 bichloride solution be used in the bladder to destroy any tumor cells thrown down because of manipulations from above. More conservative treatment has been asked for, particularly when one is dealing with neoplasms such as fibroma or myoma or lipoma, and the kidney can be spared as well as a portion of the ureter. The treatment in these cases depends upon a rapid diagnosis at the time of surgery by the pathologist. It has been stressed also that in dealing with ureteral granuloma which may be bilateral, there is danger in performing radical surgery, such as ureteronephrectomy. One may discover at a later date that the remaining kidney is impaired. The authors point out the importance of biopsy by means of rapid diagnosis at the time of surgery and thus the course of action is more rational.

Chronic irritation by calculi seems to precede a very small number of benign ureteral neoplasms. The significance of ureteritis cystica is open to much question in attempting to link it as a possible cause of ureteral neoplasm. Leukoplakia, according to Aschner, may precede the formation of calculi in some instances and be a factor in the development of a ureteral tumor. It has been suggested but not proved that the etiological factor in ureteral tumors is some carcinogenic substance eliminated through the kidneys. There is circumstantial evidence that certain dyes by inhalation may lead to the appearance of tumors of the kidney and ureter. There is direct evidence that a parasite will cause these tumors. Arsenic has been thought to be of some importance in the production of ureteral neoplasm, particularly those people who have been treated for other conditions with the chemicals.

The tumor of the ureter in this case report was apparently present for 3 years and possibly longer inasmuch as the patient was known to have complained of attacks of hematuria during a 3 year period. Although it cannot be proved absolutely that the ureteral papilloma was the sole cause of the hematuria in this man's case, the evidence points strongly to it as the etiologic factor. An interesting point is the almost negligible dilatation of the pelvis and calyces of the kidney above the ureteral obstruction. There was probably a degree of obstruction but not sufficient over a period of 3 years to have produced significant hydronephrosis.

The histologic study of the tumor confirmed the clinical course of its benign nature. There was an orderly arrangement to the palisade architecture of the tumor and the cells were of about the same size and shape with a rare mitosis. There was no breaking through the basement membrane. The richly vascularized connective tissue stalks of the tumor explain the hematuria. The consensus of opinion was that this represented a benign neoplasm and showed none of the features which are seen in carcinoma, such as variation in size and shape of cells, invasion of the stalk, hyperchromatic nuclei, and many mitotic figures.

The potential malignancy of benign ureteral neoplasm, particularly the transitional cell papilloma, has been stressed by many. Some have used a terminology and classification in which benign papillomata of the transitional cell type have been called grade 1 carcinoma. There are histologic criteria of carcinoma which a benign papilloma does not have and this case report utilizes the classification of "benign papilloma" and reserves the diagnosis of carcinoma when there is invasion of the stalk of the neoplasm or base, or when the malignancy characteristics of the cells are such as to warrant such a diagnosis. The study of numerous microscopic sections in dealing with urinary tract neoplasms cannot be emphasized enough in diagnosis.

Benign neoplasms of the ureter may be classified into : A) Epithelial: papilloma; and B) non-epithelial: myoma, lipoma, fibroma, hemangioma, etc. Cases of mixed tumor have been reported; in 1 a tumor of the ureter was found at autopsy, which was composed of smooth muscle, epithelium, connective tissue and bone. The second was classed as a fibromyoma. The papilloma may be pedunculated or may be sessile; in the former instance, the complication of intussusception should be kept in mind. Also, due to obstruction, hydroureter and hydronephrosis may develop. The nonepithelial neoplasms may arise in the wall and compress the ureter or may arise from the outer coats and encircle the ureter.

The transitional cell papilloma shows numerous branching and stalked processes with a palisade arrangement to the cells which are of the same size and shape, show few or no mitoses and no hyperchromatism. There is no invasion of the stalk or base of the neoplasm.

SUMMARY AND CONCLUSIONS

A report of a primary, benign, ureteral transitional cell papilloma is added to the literature, and the symptoms, diagnosis and treatment discussed.

A total number of 32 cases, including this case report, of benign ureteral neoplasms, primary, which have been confirmed by microscopic examination, is recorded.

The separation of benign papilloma from carcinoma is made in this report, and the criteria for such a diagnosis listed.

A suggestion for more conservative surgery in treatment when one is dealing with connective tissue tumors such as lipoma, myomas, etc., is made; this will often result from consultation with the pathologist at the time of operation.

The importance of accurate investigation of the ureter as well as the kidney and bladder in cases of hematuria is emphasized. This is accomplished by ureteropyelogram.

The authors thank Dr. H. Edward MacMahon, Tufts College Medical School, for his aid in preparing this report.

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DIRECT MANIPULATION OF URETERAL STONES THROUGH THE URETHRA

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Moderately large stones in the extreme lower portion of the ureter are often difficult or impossible to manipulate by ordinary cystoscopic methods. When surgery is resorted to, one of three routes is usually followed: (a) extraperitoneal approach through a Gibson or midline incision, which may be quite a formidable procedure in some patients; (b) by vaginal ureterotomy; or (c) when the stone is extremely low or protruding into the bladder, by cystotomy and removal through the bladder.

Stones of this type are more frequently seen in women. There are cases encountered in which any type of open operation may be undesirable. Occasionally these patients are acutely or dangerously ill. There are others in whom repeated operations may be necessary because of recurrences or multiple calculi higher in the ureter or in the renal pelvis.

In dealing with such cases we have used the method to be described in over 20 cases of stone in the lower inch or two of the ureter. We have been surprised at the ease with which most of them have been removed. While one of us employed the method almost 10 years ago, we have found no mention of it in the literature nor have we encountered a urologist who has used it.

Under a low spinal or pentothal anesthesia a No. 21 Brown Buerger or Ravich cystoscope is passed and the bladder inspected with the observation telescope. Along the side of the cystoscope an alligator forceps 8 inches long is introduced directly into the bladder. The orifice on the affected side is located and the forcep manipulated so as to bring the tip into the field of vision. It is then placed in the orifice which is dilated by opening and closing the jaws. The stone is then grasped and removed. See figure 1.

Our results have been so satisfactory that recently we have removed stones from the ureters in two men, employing external urethrotomy to introduce the cystoscope and forcep. In 2 cases of tumor of the bladder in women we have found it convenient to use an electrode passed alongside the cystoscope for extensive fulguration. The rigid electrode with ball tip formerly used with the old Collins electrotome is suitable for this procedure.

In the earliest days of endoscopy or cystoscopy David Newman in 1883 described a method of passing a small electric bulb lighted with batteries into the bladder viewing the interior and catheterizing the ureters through a cone-shaped telescope. Since the development of the cystoscope we find no reference to this direct method of manipulation within the bladder having been used.

The simplicity of the procedure may commend it for use in various situations that are, for some reason, not easily carried out through a cystoscope.

In the cases we have treated there have been no untoward results and only reasonable care seems to be necessary in carrying out the procedure. The

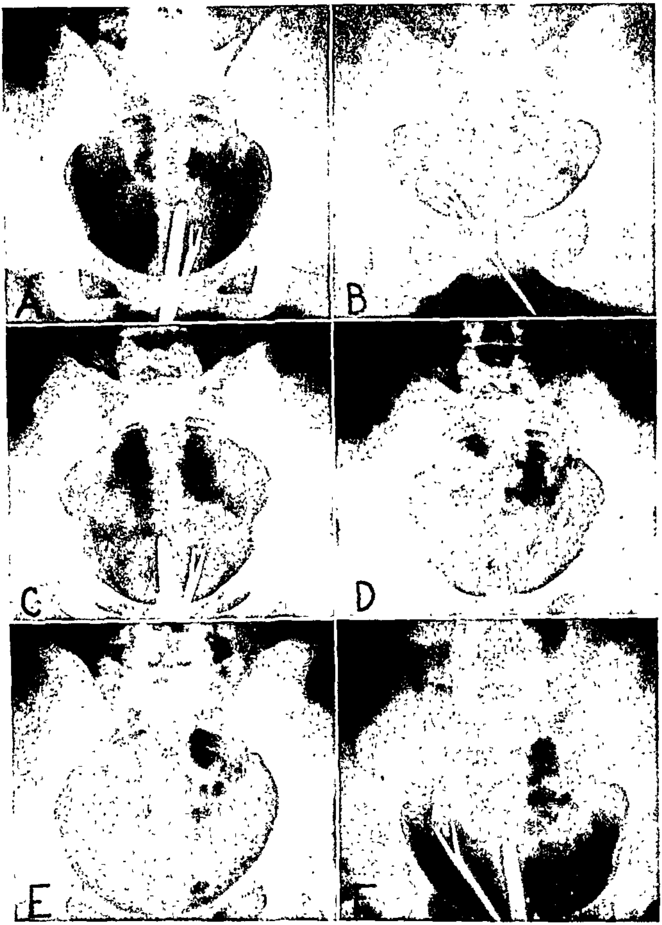

FIG. 1. *A*, Showing forceps grasping stone in lower left ureter. *B*, Cystoscope has been removed and a stone is being extracted from right ureter. *C*, Stone being removed from left ureter. *D*, Multiple stones in left ureter, all of which were removed by this method in three attempts over the period of 10 days. *E*, Large stone in right ureterocele, orifice of which was dilated and stone removed by this method. *F*, Showing length to which forceps may be introduced into ureter. In this case stone was pushed up out of reach of forceps, but was removed several days later after it had come down to its original position.

method is presented because we believe it can be used to considerable advantage in the types of cases mentioned.

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TWENTY-SECOND CASE OF XANTHINE URINARY CALCULUS

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Until 1937 only 15 cases of xanthine urinary calculi had been reported. These were reviewed by Kretschmer. According to Hinman, xanthine calculi are "very rare." The number gradually increased to 19, and recently Gersh and Meltzer reported two more, bringing the total to 21. Only by careful and persistent analysis of all urinary calculi, whether they may be surgically removed or spontaneously passed, will the occurrence of xanthine urinary calculi cease being "very rare." The case which will be cited is an example of the result of meticulous laboratory analysis performed under difficult conditions.

CASE REPORT

A 21 year old white soldier was admitted to the Thirty-First Station Hospital, which was set up on an island in the South Pacific. His chief complaint was intermittent gross hematuria over a period of 7 years. He had not informed his draft board of this symptom. Also, there was diminution in the size and the strength of the urinary stream, frequency, nocturia 2 to 3 times, and an occasional sudden stoppage of the stream.

The urine was acid, contained 10–20 white blood cells, 5–10 red blood cells per high power field; otherwise negative.

Intravenous urograms revealed a faint oval shadow, 2 by 1 cm., lying in the region of the bladder. There were no other opaque shadows. The calyces and pelves were well filled, normal in appearance and emptied promptly.

Under spinal anesthesia, cystoscopy disclosed a smooth oval calculus on the floor of the bladder. Cystitis was present. The calculus was grasped with a lithotrite, and under strong pressure, broken into small fragments which were further reduced in size and removed from the bladder. After a week of bladder irrigations, a second cystoscopy revealed no residual fragments. The patient was discharged after 3 more days to rejoin his unit, which left the island; so he could not be followed.

The calculus was light brown externally, and was white and laminated on the interior. Chemical analysis was performed in the Thirty-First Station Hospital laboratory under the direction of Major Evril Larssen, M.C., formerly of the University of Minnesota. Tests for all of the usual constituents of calculi were negative (including uric acid). The test for xanthine was positive. It was carried out on multiple portions of the calculus.

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IMPROVED PYELOGRAPHIC RESULTS IN URETERO-INTESTINAL ANASTOMOSIS

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Although some 60 techniques for uretero intestinal anastomosis have been proposed, an ideal procedure has not been perfected. Such a method would result routinely in no leakage at the anastomosis, normal kidney function, no hydronephrosis (a manifestation of obstruction), and of course, no general complications or mortality. The surgeon's aim is not only to have living patients but also to seek functional results which will fulfill the above criteria, particularly in regard to "hydronephrosis" which is a major problem.

A review of the literature did not reveal significant statistics on the pyelographic results following uretero intestinal anastomosis, but the impression was unavoidable that although the occasional postoperative pyelogram was normal, the usual result was not good. On the Cornell urological service the transperitoneal Coffey I operation was used routinely 96 times on 48 patients who had normal preoperative pyelograms. Six deaths occurred following the procedure with one attributed directly to the local effects of the operation. In this group, 25 per cent of the postoperative pyelograms were normal, and 4 patients (8.3 per cent) had normal pyelograms bilaterally.

In the series reported here, the Coffey I transperitoneal method was also used, but the author concentrated attention on the various steps of a uretero intestinal anastomosis in the hope that poor pyelographic results, one of the weakest features, could be eliminated. As this has been largely realized, a report on the technique used with a demonstration of the pyelograms appears worthwhile. Though the series is small, it is significant that 80.9 per cent of the postoperative pyelograms are normal and 7 of the 11 patients (63.6 per cent) have normal pyelograms bilaterally. The present group of the author's cases was no more selected than the previous series. Other members of the staff have also improved their pyelographic results by following the technique to be described. One operator has transplanted 12 consecutive ureters, obtaining 9 normal pyelograms and 4 of the 6 patients had normal postoperative pyelograms bilaterally when last examined.

Before proceeding to a description of the technique, preoperative preparation and postoperative care should be discussed. In addition to a complete urological investigation, a diagnostic barium enema was obtained to ascertain the condition of the large bowel. Adequacy of the anal sphincter was determined. A low residue diet, 2 gm. sulfasuxidine q.i.d., tap water enemas (until clear) and 250 cc. magnesium citrate on alternate days was the routine (5 days) used to prepare the bowel and render it as bacteriologically "clean" as possible. Enemas until clear were given on the evening and morning prior to operation. Postoperatively early ambulation was stressed. Constant drainage by rectal tube was maintained for 7 to 10 days. Routine Wangensteen suction of the stomach by Levine tube was used and discontinued as indicated. The diet was gradually increased to low residue and maintained for 2 weeks. Chemotherapy was employed routinely after operation.

Intratracheal ether provided excellent relaxation. A liberal right lower rectus or transverse incision at the level of the anterior spines was used, the latter being preferred in obese individuals as better exposure was usually obtained for the left transplant. The transperitoneal approach was used in each instance and the ureter implanted longitudinally into the bowel as in Coffey's first operation. It would appear that an excellent pyelographic result can be obtained in uretero-intestinal anastomosis, without adding new hazards, when the principles to be mentioned are followed.

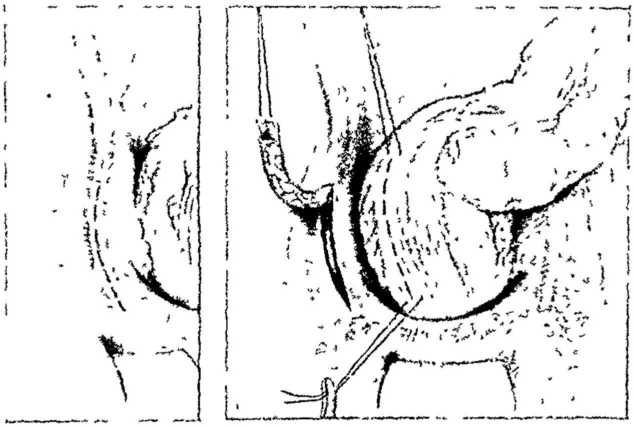

Fig. 1. *A*, Line of incision to expose right ureter. *B*, Right ureter prepared for implantation. Dotted line designates proposed site for trough.

TECHNIQUE

Mobility of the rectosigmoid. The rectosigmoid should be examined at the beginning of the operation. A mobile rectosigmoid is of utmost importance, for if the ureters, particularly the right, are to take a normal course the sigmoid must be free enough to lie without tension in the right or left side of the pelvis. Immobility due to a short mesentery or obesity can usually be corrected: for example, in transplanting the right ureter, the parietal peritoneum was incised just to the left of the rectosigmoid. In principle, the ureter was prevented from taking an "uphill" course and the bowel made to fit the course of the ureter, and not vice versa.

Minimal but adequate freeing of the ureter (figs. 1, A, B; 3, D). As little as possible of the ureter is freed. The length dissected should be just enough to allow a smooth, nonangulated course, without tension, from the lowest point of retroperitoneal attachment to the upper end of the trough. Excessive dissection increases the possibility of angulation and of later periureteral fibrosis from trauma to the ureter and peritoneal tissues. A transplant can usually be executed by freeing no more than 4 cm. When cutaneous ureterostomies became necessary in 2 patients in the earlier series after 3 and 6 months, the obstruction was found at the pelvic brim and not at the anastomotic site. The ureter was dilated to this point. To avoid such an occurrence and to allow as much of the ureter as possible to retain its normal course and blood supply, the posterior peritoneum is opened 4 cm. below the bifurcation of the common iliac artery. In most cases the ureter is found with ease at this point, but in obese individuals

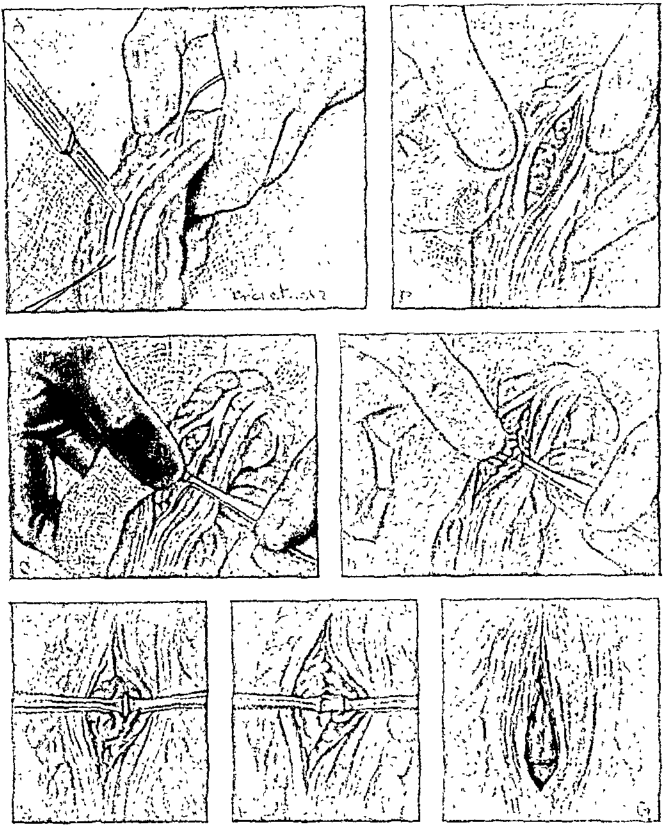

Fig. 2. *A*, Incising bowel longitudinally. *B*, Submucosa exposed, few circular fibres left intact. *C*, *D*, Note position of hands and forceps as left lateral flap is being started and made. *E*, *F*, Note position of forceps and method of widening flap. *G*, Trough completed; lateral flaps spread, exposing transverse incision in mucosa.

preliminary catheterization of the ureters, although seldom necessary, may be helpful.

Once identified, the ureter with its surrounding periureteral fat was freed to the bladder with as little trauma as possible. If there was no infection in the upper urinary tract, only one right angled clamp was placed at the ureterovesical junction to preserve as much ureter as possible. The ureter was then divided just proximal to the clamp and the lower stump transfixed with a chromic No. 1 catgut suture. The end of the ureter was made into a "fishmouth" for about ½ cm. and two-thirds of the lower flap removed to avoid the possibility of its folding upwards into the trough when the ureter is inserted into the bowel lumen. A single mattress suture of chromic 0 catgut was then passed twice through the dorsal flap, and the free ends of this suture threaded with a curved intestinal needle. The ureter was then wrapped in moist saline gauze and attention directed to the bowel.

Preparation of the trough (*fig. 2*). This is probably the most important step in the procedure, for there must be no obstruction to the ureter as it traverses the bowel, not only from the early edema and induration, which will subside, but also from the later fibrotic changes which are permanent. Although the use of the longitudinal incision has been criticized by some writers as injuring the blood supply of the bowel, this seems to have no significance in the present series. Moreover, if the trough is made carefully, injury to the larger vessels with subsequent hematoma is avoided.

The rectosigmoid is re-examined and a suitable site for implantation selected, as low as possible for the right ureter. This site must naturally fit the area from which the ureter was dissected when all traction on the bowel is released. A taenia (right taenia for the right ureter and vice versa) was routinely used as the better development of the muscular layers permits easier construction of the lateral flaps. One traction suture of fine silk was placed through the taenia at the lower end of the selected site and another was placed 4 cm. above to outline the length of the proposed trough.

Holding the bowel with moist saline gauze, a longitudinal incision was made down through most of the circular muscular fibers. However, a very thin layer of circular fibers was left intact with the mucous membrane "pouting out" in a few places. This step is important as it makes formation of the trough simple.

Grasping the bowel gently with the gauze covered hand and with the aid of a fixation forceps, a flap was started in the incised portion of the bowel where there were still a few intact circular fibers. The sero-muscular layer was "peeled" back in a plane between the severed and intact circular fibers, at right angles to the line of the incision. The position of the hand holding the bowel is important, as the fingers are used as a fulcrum for the forceps to act upon. The fingers should be manipulated simultaneously with the forceps as the trough is being constructed throughout its entire length. Using this method a flap 1 cm. in width can be raised in a few minutes. After this had been obtained, it was further widened by grasping the lowermost portion of the inner aspect of the flap with 1 fixation forceps and the adjacent mucous membrane with another, and continuing to peel it back by spreading the 2 forceps apart. This maneuver was carried along the full length, increasing the width by at least another ½ cm.

An identical procedure was carried out in constructing the opposite flap, except that the hands were interchanged. The flaps should be at least 1½ cm. wide on each side; this cannot be too strongly stressed and the above technique accomplishes it with a minimum of trauma, effort and time. After a satisfactory trough has been made, the remainder of the circular fibers were severed.

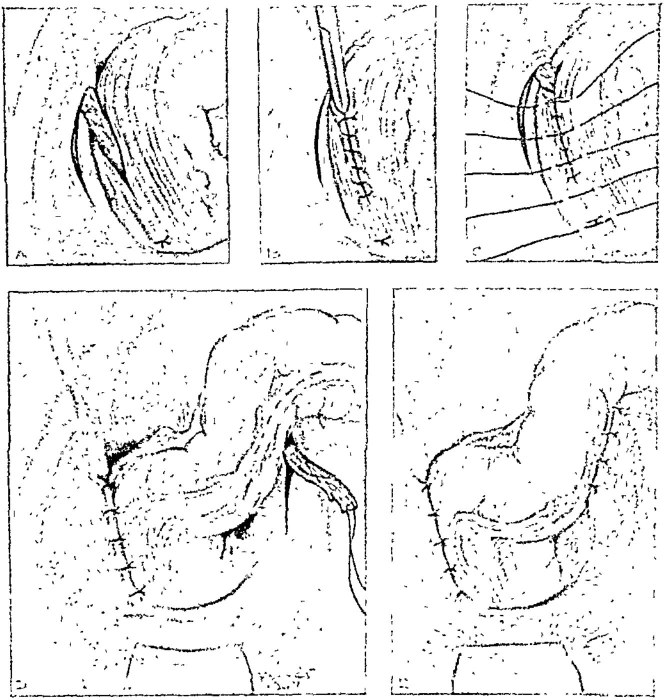

FIG. 3. *A*, Ureter implanted in bowel, anchoring stitch tied. *B*, Edges of lateral flaps closed with continuous suture. Note clamp. *C*, Interrupted inverting silk sutures placed. *D*, Anastomosis extraperitonealized. Left ureter prepared for implantation. Dotted line designates proposed site of trough in left taenia. *E*, End result. Ureters implanted and anastomosis extraperitonealized.

Implantation of the ureter into the bowel (figs. 2, G; 3, A, B, C). A transverse incision was made through the mucosa in the lower end of the trough, large enough to accommodate the bulk of the ureter loosely, that is, not a pinpoint opening. The 2 ends of the mattress suture in the dorsum of the fishmouth were brane. This was done in order to take up "slack" and leave as little free or redundant ureter between its exit from the posterior peritoneum and its entrance to the uppermost portion of the trough.

The ureter lay loosely in the trough when the edges of the lateral flaps were brought together with a continuous 0000 chromic ureteral catgut suture. The last stitch was tied over a Kelly clamp, just short of the upper end of the trough, to prevent any possible constriction at the proximal end. This suture line and anchoring stitch were then inverted with interrupted fine silk sutures, which were placed about 1 cm. on either side of the longitudinal incision and tied loosely.

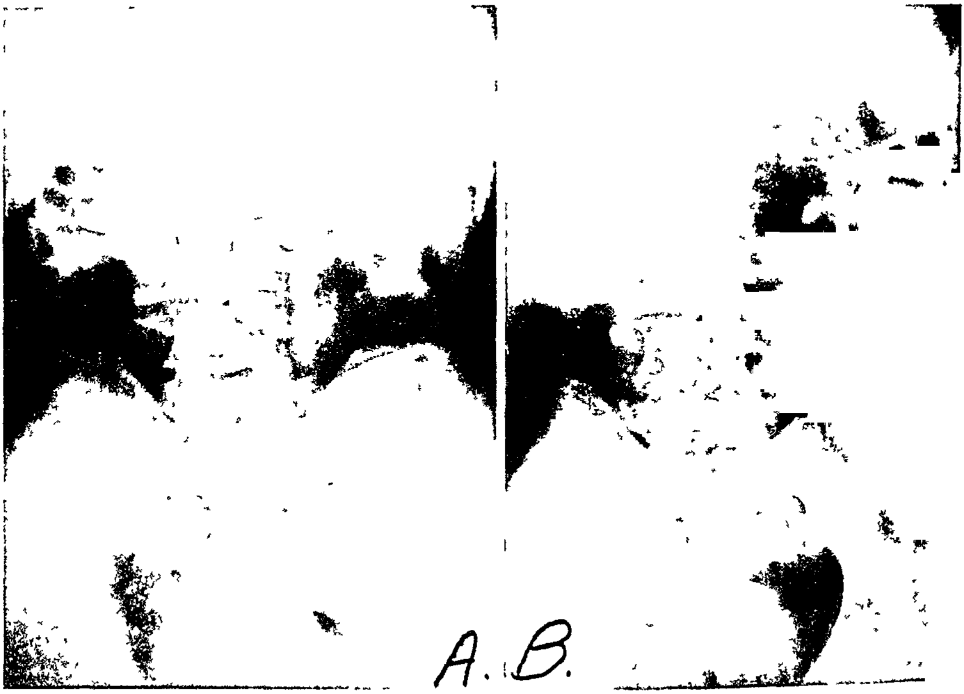

FIG. 6 Case 5. N.Y H 380577. R.T., male aged 59. Diagnosis Carcinoma of bladder *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram at 7 weeks

The ureter was observed constantly for dilatation as each stitch of the suture lines was being placed. If dilatation occurred, the constricting suture (usually the last one) was removed.

Immobilization by partial extraperitonealization (*fig. 3, D, E*). The ureter was then restored to its normal position by placing the bowel in the correct location in the pelvis and the site of the anastomosis fixed by partial extraperitonealization. This was accomplished by "tacking" a wide flap of parietal peritoneum over the anastomosis and burying the latter completely with several fine silk sutures.

The ureter was finally examined to make certain that 1) it functioned well, 2) no dilatation or tension existed; 3) no excess or redundant ureter was present between its exit from the posterior peritoneum and entrance to the proximal end of the trough.

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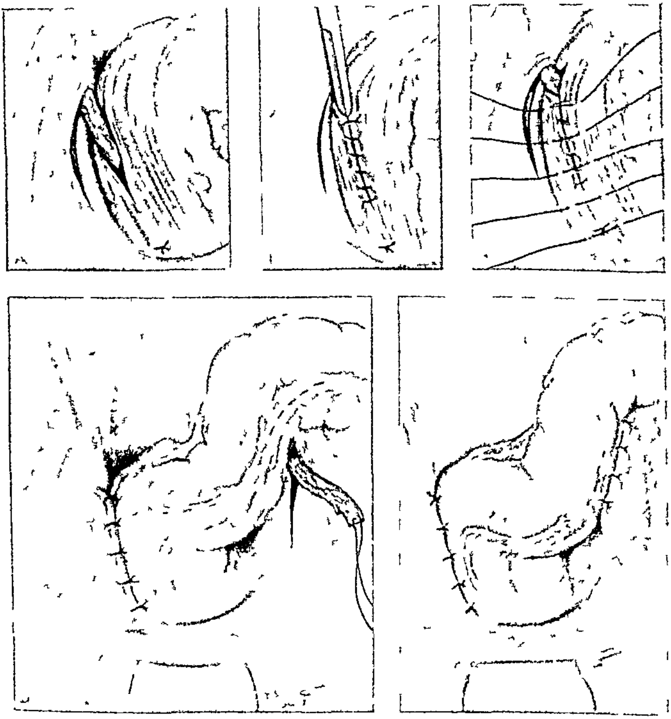

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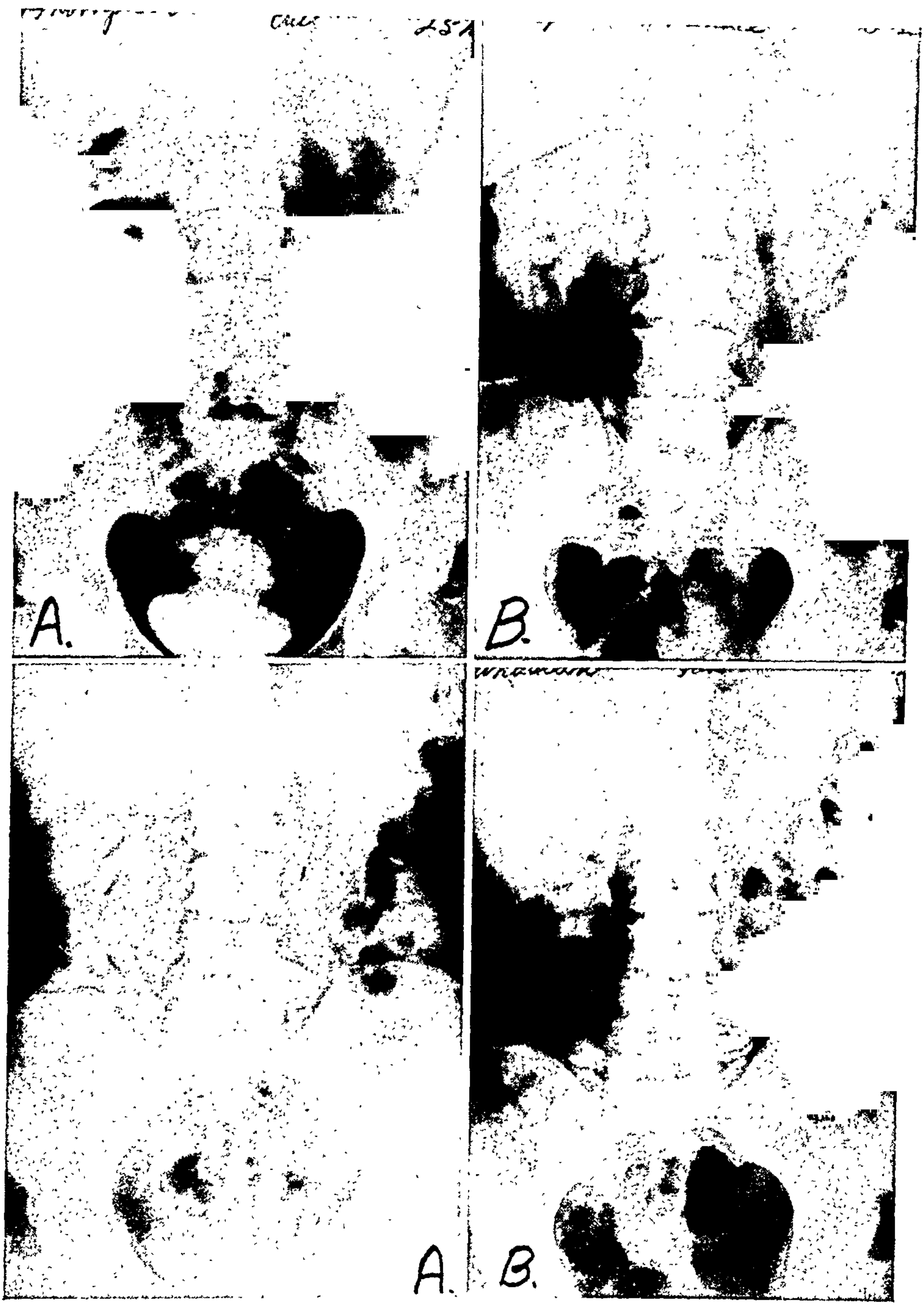

FIG. 4. (Upper), case 1. N.Y.H. 359890, F. T., female age 57. Diagnosis: carcinoma of urethra. *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram, 9 weeks.

(Lower), case 2. N.Y.H. 10076S. V. M., female aged 67. Diagnosis: radiation cystitis. *A*, Preoprative intravenous pyelogram; surgical absence of left kidney. *B*, Postoperative intravenous pyelogram, 6 weeks.

then introduced through this incision and passed out through the full thickness of the bowel wall at least 1 cm. below. This suture was tied loosely after the

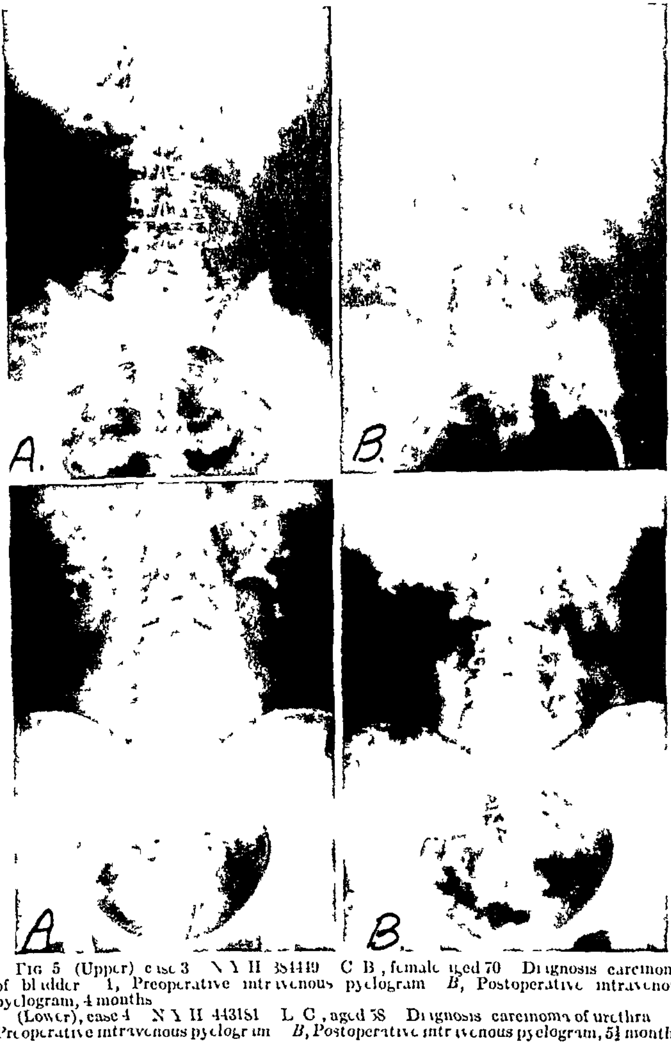

Fig 5 (Upper) case 3 N Y H 384419 C B, female aged 70 Diagnosis carcinoma of bladder A, Preoperative intravenous pyelogram B, Postoperative intravenous pyelogram, 4 months

(Lower), case 4 N Y H 443181 L C, aged 58 Diagnosis carcinoma of urethra A, Preoperative intravenous pyelogram B, Postoperative intravenous pyelogram, 5½ months

ureter had been drawn into the bowel lumen The distance of 1 cm. was variable The ureter has often been sutured 2 cm. below the opening in the mucous membrane. This was done in order to take up "slack" and leave as little free or redundant ureter between its exit from the posterior peritoneum and its entrance to the uppermost portion of the trough.

The ureter lay loosely in the trough when the edges of the lateral flaps were brought together with a continuous 0000 chromic ureteral catgut suture. The last stitch was tied over a Kelly clamp, just short of the upper end of the trough, to prevent any possible constriction at the proximal end. This suture line and anchoring stitch were then inverted with interrupted fine silk sutures, which were placed about 1 cm. on either side of the longitudinal incision and tied loosely.

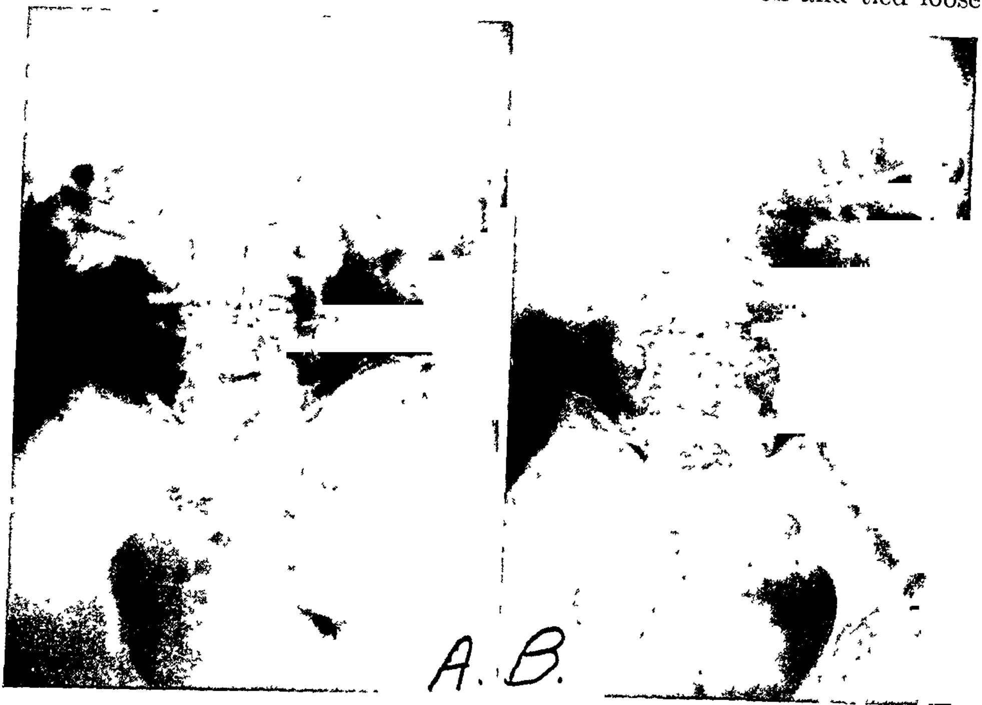

FIG. 6. Case 5. N.Y.H. 380577. R. T., male aged 59. Diagnosis Carcinoma of bladder *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram at 7 weeks.

The ureter was observed constantly for dilatation as each stitch of the suture lines was being placed. If dilatation occurred, the constricting suture (usually the last one) was removed.

Immobilization by partial extraperitonealization (*fig. 3, D, E*). The ureter was then restored to its normal position by placing the bowel in the correct location in the pelvis and the site of the anastomosis fixed by partial extraperitonealization. This was accomplished by "tacking" a wide flap of parietal peritoneum over the anastomosis and burying the latter completely with several fine silk sutures.

The ureter was finally examined to make certain that 1) it functioned well, 2) no dilatation or tension existed; 3) no excess or redundant ureter was present between its exit from the posterior peritoneum and entrance to the proximal end of the trough.

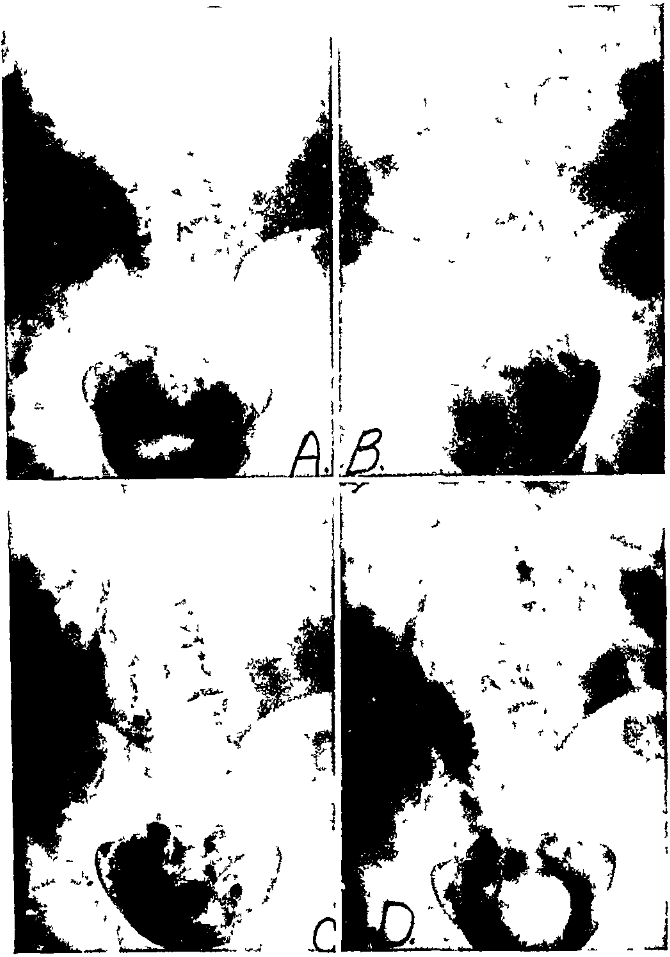

Fig. 7. Case 6. N. Y. H. 46120. A. M., male aged 62. Diagnosis: carcinoma of bladder. Evolution of postoperative intravenous pyelograms. *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram, 2 weeks. *C*, Postoperative intravenous *pyelogram, 2 months. D, Postoperative pyelogram, 4 months. Note dye in bowel.*

The left ureter was implanted in the same manner as the right, though slightly higher. Often, it was placed in the pelvic surface of a hanging loop of redundant sigmoid.

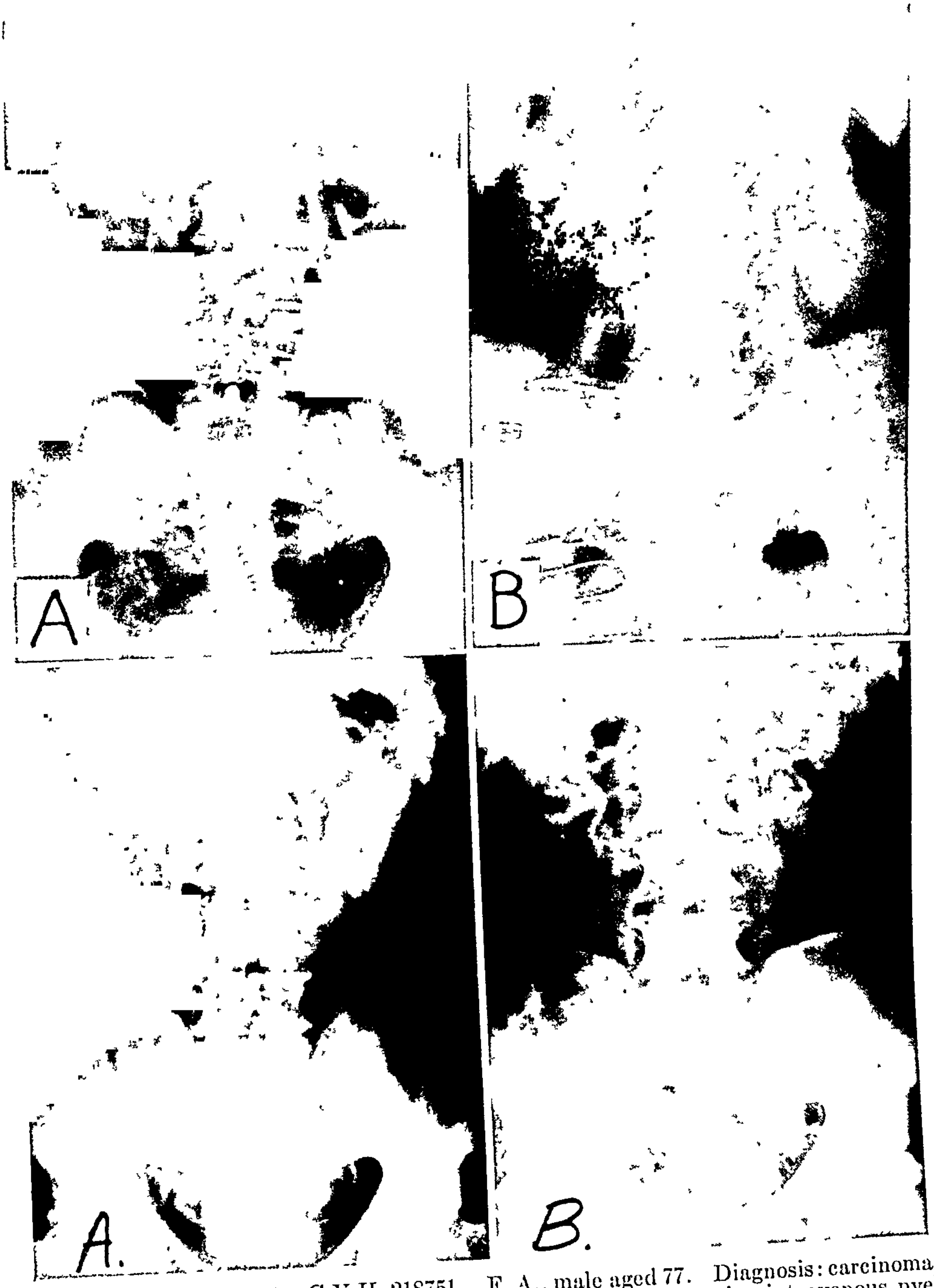

Fig. 8. (Upper), case 7. C.Y.H. 218751. F. A., male aged 77. Diagnosis: carcinoma of bladder. *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram, 5 weeks.

(Lower), case 8. N.Y.H. 455235. A. K., male aged 62. Diagnosis: carcinoma of bladder *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram, 3 months.

RESULTS

Following the above technique the author has transplanted both ureters simultaneously in 12 consecutive patients, whose ages varied from 57 to 77, fiv

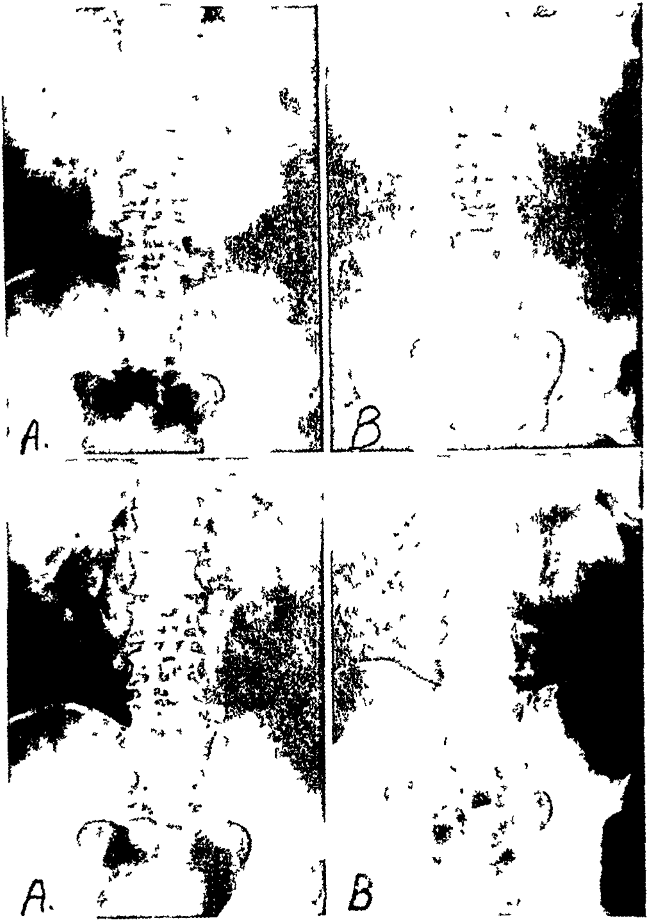

Fig. 9 (Upper) Case 4. N.Y.H. 434979. A. G., male aged 76. Diagnosis: carcinoma of bladder. A. Preoperative intravenous pyelogram. B. Postoperative intravenous pyelogram 4 months.
(Lower) Case 9. Longest followed case. A. Preoperative intravenous pyelogram. B. Postoperative intravenous pyelogram (10 minutes) 11½ months. Note dye in bowel.

being over 70. There was 1 death following the procedure. One other patient (fig. 8, case 7) died subsequent to a total abdominoperineal cystectomy, but survived the anastomosis without complications. The fatality following the anas-

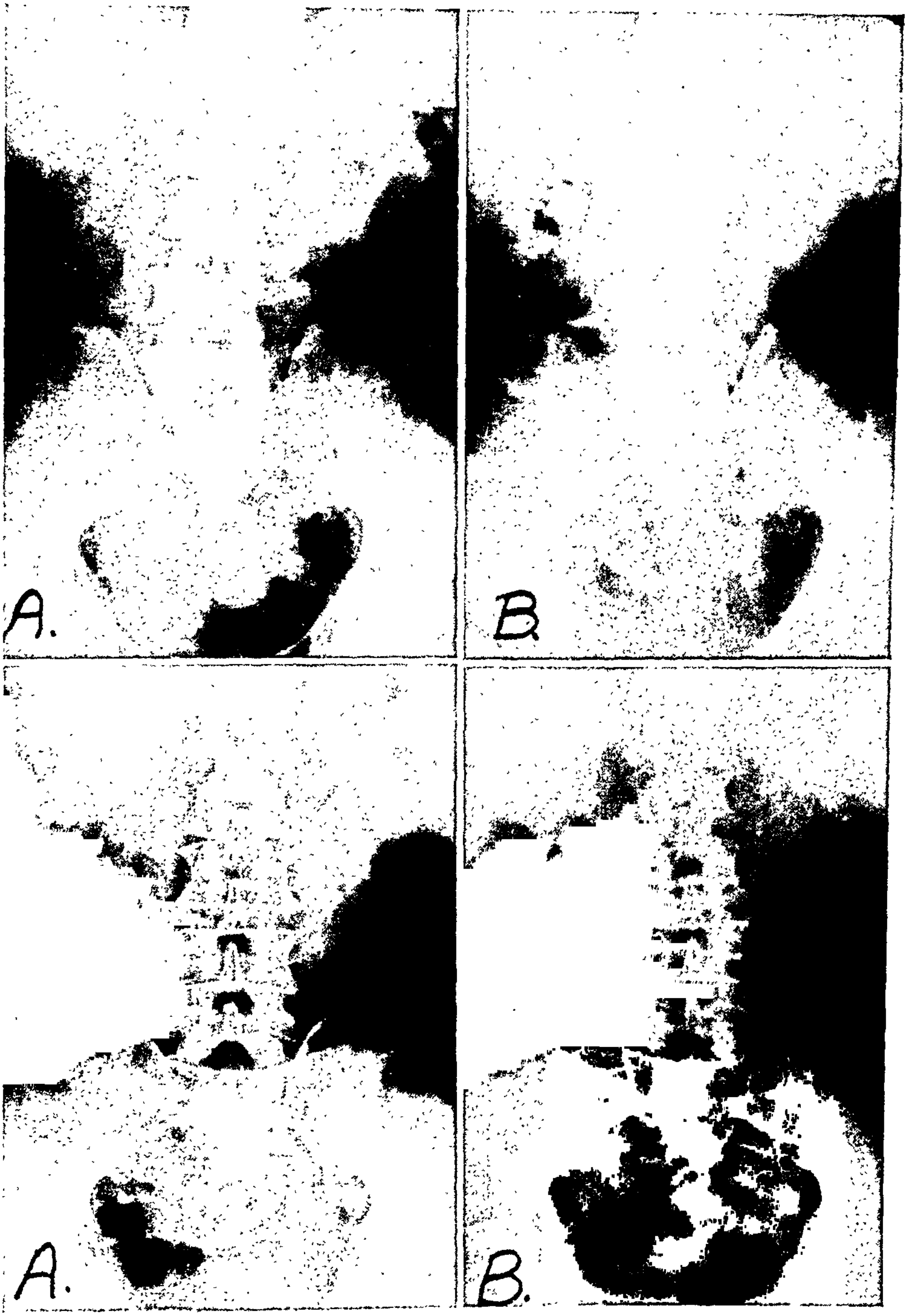

FIG. 10. (Upper), case 10. N.Y.H. 442515. W.M., male aged 75. Diagnosis: carcinoma of bladder. *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram, 7 months.

(Lower), case 11. N.Y.H. 433802, J. B., male aged 63. Diagnosis: radiation cystitis. *A*, Preoperative intravenous pyelogram. *B*, Postoperative intravenous pyelogram, 2 months.

tomosis occurred suddenly on the sixth postoperative day in the case of a 72 year old male, who prior to that time had been up and about, had a urine output over 1000 cc daily and had maintained a normal blood urea nitrogen. At autopsy there was no leakage of the anastomosis and no hydronephrosis or hydroureter, but death was due to coronary occlusion. A postoperative pyelogram had not been obtained at this early date and so there remain 21 individual consecutive transplants examined radiologically after operation (1 patient had a previous nephrectomy). There were no serious (nonfatal) complications or attacks of pyelonephritis. Though an occasional brief rise in the blood urea nitrogen was observed, none of these patients had a permanent elevation, in fact, 3 are consistently lower than preoperatively. No diversion other than uretero-intestinal anastomosis has been done, or thought indicated.

TABLE 1. Classification of pyelograms

	RIGHT	LEFT
Case 1 (fig. 4)	Poor (grade 3 Hydronephrosis)	Normal
Case 2 (fig. 4)	Poor (grade 3 Hydronephrosis)	Previous nephrectomy
Case 3 (fig. 5)	Normal	Intermediate (Detectable Hydronephrosis)
Case 4 (fig. 5)	Normal	Normal
Case 5 (fig. 6)	Normal*	Intermediate (Grade 1 hydronephrosis)
Case 6 (fig. 7)	Normal	Normal
Case 7 (fig. 8)	Normal	Normal
Case 8 (fig. 8)	Normal	Normal
Case 9 (fig. 9)	Normal	Normal
Case 10 (fig. 10)	Normal	Normal
Case 11 (fig. 10)	Normal	Normal

Number of ureters transplanted	21
Normal postoperative pyelograms	17 (80.9%)
Intermediate postoperative pyelograms	2
Poor postoperative pyelograms	2
Non-functioning kidneys	0

* This patient had a malignant carcinoma of the bladder and died within 6 months after the diagnosis was made. Intestinal transplants were done for palliation. X-ray submitted represents the 7 weeks postoperative film. Patient would not return to the hospital for further follow up due to severe pain. As the right hydronephrosis remained unchanged, if anything, decreased, the pyelogram is termed normal in this particular case.

Intravenous pyelograms have been made at frequent intervals. Usually a grade I hydronephrosis with excellent excretion of dye exists 2 to 3 weeks postoperatively, although it is not rare to see a normal pyelogram at this time. In most cases, the pyelograms continue to improve over the next 14 to 16 weeks, before becoming stationary; apparently, this is the period necessary for the edema to subside. Figure 7, case 6, illustrates the evolution of the pyelograms in the early postoperative period. The longest follow-up in this series is 11½ months and the pyelograms have remained normal (fig. 9, case 9).

The pyelograms in this series have been classified as good, intermediate, or poor. Pyelograms presenting a normal calyceal pattern without dilatation and with prompt excretion of dye are considered good; detectable to grade I hydronephrosis but with good excretion of dye, intermediate; and all others, poor. Using this strict, arbitrary standard, 17 of the 21 individual transplants, or 80.9 per cent are classified as good, 2 as intermediate and 2 as poor. All postoperative pyelograms illustrated represent the 10 minute films. Details of the pyelographic results are shown in table I.

CONCLUSIONS

An ideal pyelographic result, following uretero-intestinal anastomosis can be obtained in a much larger percentage of cases than has been thus far reported. Using the technique outlined above, the percentage of normal pyelograms in the original Coffey I operation has been increased from 25 to 80.9. The present series is small, but the marked degree of improvement is significant. Other members of the staff have also improved their results. It is the author's belief that the close observation of the following principles were largely responsible for the improvement:

a) Mobility of the rectosigmoid: The rectosigmoid should be freely moveable and if not, mobilization is indicated. The bowel should be made to fit the course of the ureter and so prevent the latter from taking an "uphill" course.

b) A minimum of ureter is freed: In this way angulation is avoided and the ureter allowed to retain as much of its normal retroperitoneal course as possible, and unnecessary injury to its blood supply prevented.

c) Formation of an adequate trough: This is probably the most important step. The trough must accommodate the ureter loosely, and be able to compensate not only for the early edematous reaction, but also the later, more permanent fibrotic changes. This is accomplished by the gentle construction of a very wide trough, which has routinely been obtained by the technique described above. Each lateral flap should be at least 1.5 cm. in width.

d) Avoidance of excessive or redundant ureter between its exit from the posterior peritoneum and entrance into the trough is important, but at the same time, tension must be absent.

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CARCINOMA OF THE URINARY BLADDER A PATHOLOGIC STUDY WITH SPECIAL REFERENCE TO INVASIVENESS AND VASCULAR INVASION[1]

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It was believed that a study of a sizable group of surgically removed carcinomas of the urinary bladder might be worth while if the accompanying bladder were available also Many investigations have been made on vesical neoplasms by utilization of tissue removed transurethrally but in such studies only a portion of the underlying bladder, at most, can be studied Information which the surgeon obtains from the pathologist is oftentimes woefully inadequate as applied to the method of treatment which should be employed in such a case Further more, when surgical therapy is given such a patient suffering from a carcinoma, the factors entering into the prognosis have been vague, much more vague than in cases of carcinoma elsewhere in the body

Several excellent studies have been reported concerning factors which govern prognosis in carcinoma of the urinary bladder Broders in 1922 showed the influence of the factor of histologic grade on the prognosis Further proof of the influence of the factor of grade on the survival rate of patients suffering from carcinoma of the urinary bladder is evident from the reports of the bladder tumor registry of the American Urological Association (1934 to 1936, inclusive) It is obvious that the histologic grade of a neoplasm is not the only factor of importance This is evident elsewhere in the body as, for example, in the large bowel where it has been shown by Dukes that infiltration of the wall of the bowel and the pericolonic fat and metastasis are factors of extreme importance in the prognosis The importance of involvement of the blood and lymphatic vessels in carcinoma of the renal pelvis, in regard to prognosis, has been stressed by one of us (McDonald and Priestley). It was that study which stimulated the present one

Anatomic factors have been considered in several studies on vesical tumors Aschner in 1931 classified neoplasms of the bladder as to whether they did or did not infiltrate and as to whether they were papillary or nonpapillary On the basis of a follow-up of 3 years or longer, in the papilloma group 80 per cent of the lesions were arrested, in the papillary carcinoma group without infiltration, 54 per cent were arrested, in the papillary carcinoma group with infiltration, 18 per cent were arrested, and in the nonpapillary carcinoma group, 16 per cent were arrested His conclusions were that the presence or absence of infiltration represented a reliable guide as to the gravity of the carcinoma of the bladder

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A more recent attempt to employ infiltration as a guide to prognosis in tumors of the bladder is that of Jewett in 1944. In a study of 107 cases of carcinoma of the urinary bladder in all of which the patients had come to necropsy, particular note was paid to penetration of the wall of the bladder by the carcinoma. These cases were divided into 3 groups. The first group included those in which the tumor was confined to the submucosa. No evidence of metastasis or perivesical fixation was found in these cases. The second group consisted of those in which infiltration had extended into the muscularis but not through it. There were 15 cases in this group; distant metastatic lesions were found in 1 case and invasion of the lymphatics in another. The third group comprised those in which the carcinoma had invaded the entire muscle. Of 89 cases in this group, metastatic lesions were present in 52. In addition to these 52 cases, perivesical lymphatics were involved in 6 cases and perivesical fixation occurred in 8 cases.

In our study of the anatomic factors of importance which should merit consideration in tumors of the bladder, it was decided not to employ biopsy material. It is obvious that in material of this sort the anatomic relationship of the tumor to the vesical wall cannot be determined. It was therefore decided to utilize surgical material in which the tumor had been removed along with a portion or all of the vesical wall. This meant that in all cases utilized in this study suprapubic exploration was carried out and either segmental or total cystectomy was done. Cases in which suprapubic exploration was done and in which the tumor was fulgurated without removal of a portion of the wall of the bladder were discarded. We are not attempting to analyze the usefulness of various surgical methods and, consequently, the type of operation which has been done will not be mentioned further. This material was removed during the years 1932 to 1944, inclusive. Of necessity, the lesions do not represent consecutive vesical tumors seen at the clinic because many tumors of the bladder were treated by transurethral methods, irradiation therapy or a combination of these two. Nor do they represent consecutive series of vesical tumors in which segmental or total cystectomy was done at the clinic, because in certain cases specimens have been lost or were otherwise unsatisfactory for pathologic examination.

In all cases a block was cut through the greatest diameter of the tumor, including the entire vesical wall and the perivesical tissue. In some cases more than 1 block was cut. These were inpregnated with paraffin, sectioned in the usual way and stained with hematoxylin and eosin. In those cases in which, on histologic examination, it was thought that mucus was being produced by the tumor, mucicarmine stains were employed. In these vesical tumors we had sections made through the largest diameter of the tumor, the entire musculature coat, the perivesical fat and, where possible, the adjacent normal mucosa of the vesical wall. Histologic and morphologic study of these specimens was made without any knowledge of the clinical course of the disease. All observations were made, therefore, with as little prejudice as possible. The survival rates were calculated and all pertinent data from the clinical records were tabulated by the Section on Biometry and Medical Statistics.

CLASSIFICATION

A basic principle in histopathology has been to classify carcinomas into types, namely, squamous cell carcinoma, adenocarcinoma or transitional cell carcinoma For one reason or another this principle has frequently been avoided in the classification of tumors of the bladder We arbitrarily have defined a squamous cell carcinoma as one in which the cells are becoming keratinized or cornified (fig 1) Since there is no special stain with which to demonstrate keratin, minor degrees of keratinization can be difficult to recognize in hematoxylin eosin sections Keratin stains faintly with eosin or it may be dissolved out in the various solutions, leaving clear cytoplasm In this study, definite amounts of keratin had to be present before the tumor was classified as a squamous cell carcinoma A carcinoma was classified as adenocarcinoma when it formed acini or produced mucus The mucicarmine stain was helpful in identifying mucus A transitional cell carcinoma was one which was of neither of the first two types mentioned The majority of carcinomas of the bladder in this study were of the transitional cell type (table 1) A surprising number proved to be glandular The majority (30) of adenocarcinomas were not pure adenocarcinomas but were mixed either with squamous cell carcinoma or nonkeratinizing epithelioma (fig 2)

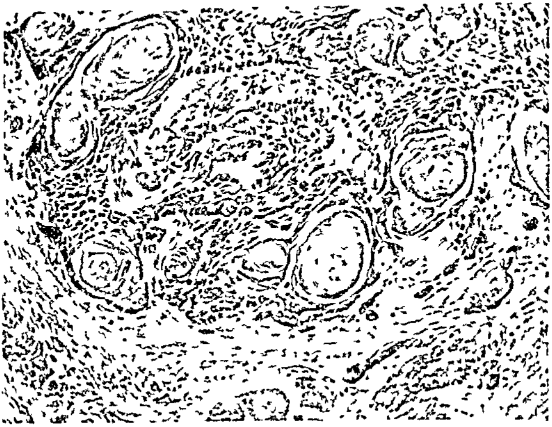

Fig 1 Squamous cell carcinoma of urinary bladder Note pearly body formation (× 95)

Of the squamous cell carcinomas (78 pure, 16 mixed squamous cell and adenocarcinoma), 93 infiltrated the wall of the bladder and one was noninfiltrative Of the 40 adenocarcinomas, pure and mixed, all were infiltrative Data on whether either venous or perineural lymphatic involvement occurred in the wall of the bladder in relation to the type of carcinoma are also summarized in table 1

The 5 year survival rates according to these various types of carcinoma are stated in table 2. The survival rate for the entire group of traced patients with these neoplasms of the bladder was 29 per cent. The survival rate for patients with nonkeratinizing epitheliomas was better than the average while the survival rate for those with squamous cell carcinoma and adenocarcinoma was poorer than the average.

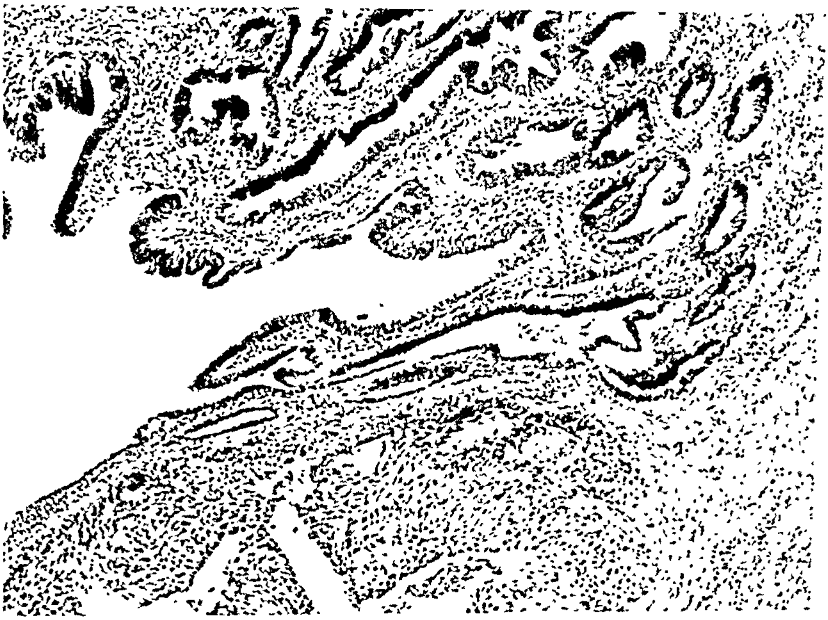

FIG. 2. Mixed squamous cell carcinoma and adenocarcinoma of urinary bladder Adenocarcinomatous portion occupies upper part (× 70).

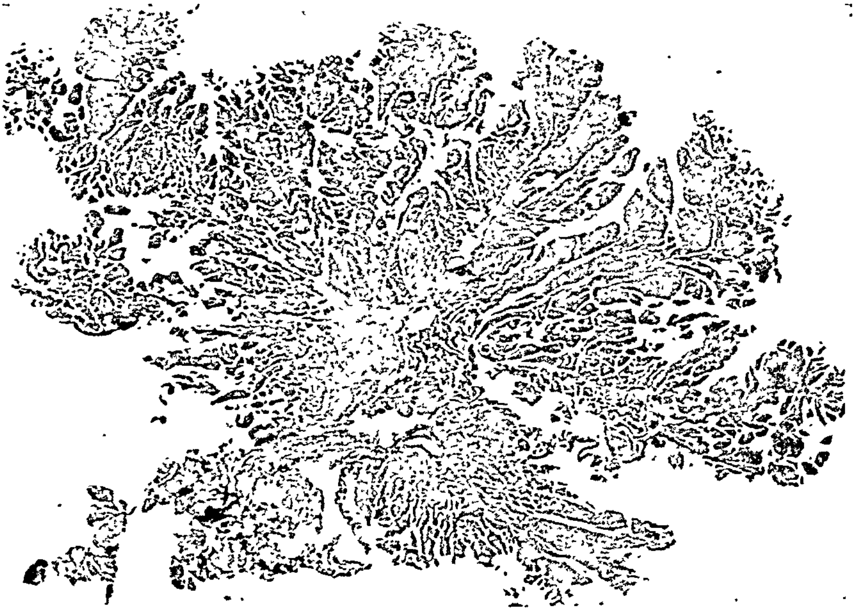

FIG. 3. Papillary transitional cell epithelium without infiltration of vesical wall (× 3).

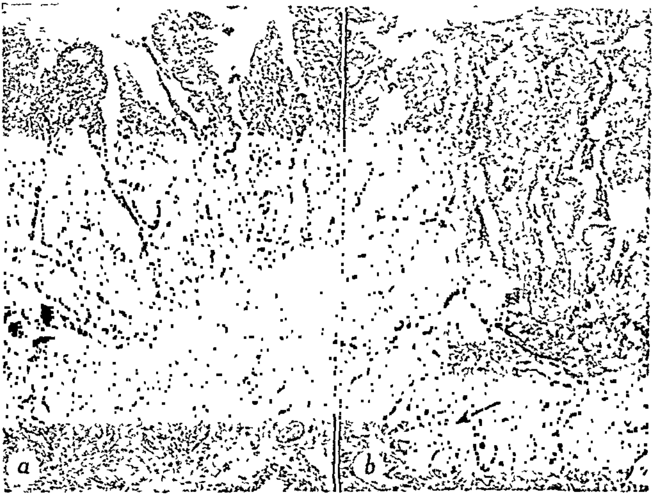

FIG. 4. Papillary transitional cell epithelioma with infiltration of the wall of the bladder. *a*, Entire tumor is of transitional cell type (× 40) *b*, Surface part of neoplasm is of transitional cell type while infiltrative portion is gland forming (see arrow) (× 42).

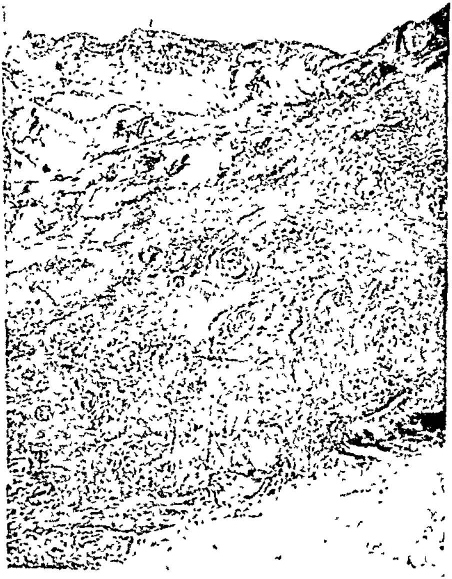

FIG. 5. Infiltrative squamous cell carcinoma of urinary bladder. There are no papillary projections on surface (× 7).

Papillary or nonpapillary carcinoma. We have divided carcinomas of the urinary bladder into 3 types: papillary carcinoma without infiltration (fig. 3), papillary carcinoma with infiltration (fig. 4*a* and *b*) and infiltrative (nonpapillary) carcinoma (fig. 5; table 3). This was done because in our experience this classification has been useful in carcinoma of the renal pelvis (McDonald and Priestley, 1944). Few of the carcinomas which have been of the squamous cell type, according to the term as we have defined it, have produced papillary projections. The adenocarcinomas have similarly shown lack of villous projections. The transitional cell carcinomas can be divided into those which are papillary and those which are nonpapillary.

TABLE 1.—*Malignancy of the urinary bladder: Type of lesion and incidence of vessel involvement*

TYPE OF LESION	CASES		VESSEL INVOLVEMENT	
	Total	Per cent	Cases	Per cent*
Squamous cell epithelioma	78	28.5	36	46.2
Transitional cell epithelioma	156	57.0	49	31.4
Adenocarcinoma	10	3.6	5	50.0
Mixed adenocarcinoma and squamous cell epithelioma	16	5.8	5	31.2
Mixed adenocarcinoma and transitional cell epithelioma	14	5.1	7	50.0
Total	274	100.0	102	37.2

* Based on the total number of cases of the type of lesion indicated.

TABLE 2.—*Carcinoma of the urinary bladder: Five year survival rates in per cent*

TYPE OF LESION	TOTAL	VESSEL INVOLVEMENT	
		Without	With
Transitional cell epithelioma	35.1	43.5	13.7
Squamous cell epithelioma (pure)	19.3	28.0	10.1
Adenocarcinoma (pure and mixed)	21.1	29.6	0
Total	29.0		

TABLE 3.—*Carcinoma of the urinary bladder: Infiltration*

	PATIENTS	PER CENT
Infiltration alone	189	69.0
Papillary with infiltration	54	19.7
Papillary without infiltration	31	11.3
Total	274	100.0

Of 189 infiltrative nonpapillary carcinomas, 118 were either squamous cell carcinoma or adenocarcinoma or combinations of adenocarcinoma with other types The remainder, 71, have been of the transitional cell type Some of these transitional cell carcinomas were probably of the papillary type originally but the projections had been burned off by transurethral fulguration There is, in other words, no way of knowing how many of these transitional cell neoplasms were originally nonpapillary As can be seen from table 3, fifty-four or 19 7 per cent of the entire group were papillary carcinomas and, on histologic examination, evidence of infiltration could be found. Some pathologists and urologists classify papillary neoplasms of the bladder into those which are benign and those which are malignant It has been our policy to group them together It is significant that the material in this study does not represent a consecutive series of vesical tumors and that many of the tumors in this papillary noninfiltrative group were treated transurethrally Only a few patients have resections of the urinary bladder It is well recognized that the majority of tumors in the bladder are of the papillary type Obviously, in this series, that is not the case

The third group of papillary tumors, made up of those which did not infiltrate the wall of the urinary bladder, comprised 31 cases or 11 3 per cent of the entire series In other words, 85 or 31 per cent of the tumors under discussion were papillary while 69 per cent were nonpapillary infiltrators Histologically, in 4 cases in the infiltrative group the lesion was graded 1 (Broders' method) All of these were adenocarcinomas We had, in this group, no grade 1 squamous cell carcinomas, all being grade 2 or higher In the group of papillary carcinomas without infiltration, 15 of 31, or 48 4 per cent, were graded 1 This is the group which would be considered as benign papillomas by many pathologists It is rare for neoplasms of this type and grade to metastasize although death may result from ureteral obstruction with subsequent infection It is obvious that there is need for a definition as to what comprises a carcinoma of the urinary bladder In the remaining 16 cases of papillary carcinoma without infiltration of the wall the lesions were graded 2 or 3 In the group of papillary tumors with infiltration there were no grade 1 lesions, all being graded 2 or higher It has been our general conception of this group that grade 1 papillary epitheliomas rarely infiltrate The survival curves for these 3 groups are given in figure 6, A Unfortunately, through a cystoscope it is often not possible to determine whether a given papillary neoplasm is or is not infiltrative

The depth of involvement of the wall of the urinary bladder in carcinoma The survival rates in this group of carcinomas of the urinary bladder which invaded the wall of the bladder has been charted according to the depth of involvement of the urinary bladder (fig 6, *B*) This group comprises those villous neoplasms which infiltrate as well as the nonpapillary infiltrating carcinomas In all there were 243 cases in which survivals could be calculated Of these, 54 belonged in the papillary group with infiltration and 189 in the nonpapillary infiltrative group The depth to which the bladder was involved has been charted according to whether the tissue between the epithelium and the muscle was involved (this has been termed submucosa) (fig 7, *a*), whether the malignant tissue extended into the muscle but not deeper (fig 7, *b*) and whether the malignant tissue extended out to the fat (fig 7, *c*) Of the entire group of lesions, 12 8 per cent penetrated only the submucosa, 53.9 per cent extended into the muscular layer and 33.3 per cent extended into the fat. Figure 6, *B* demonstrates that when the fat is involved the survival rate drops very markedly. It is in this group that the greatest amount of vascular involvement occurs.

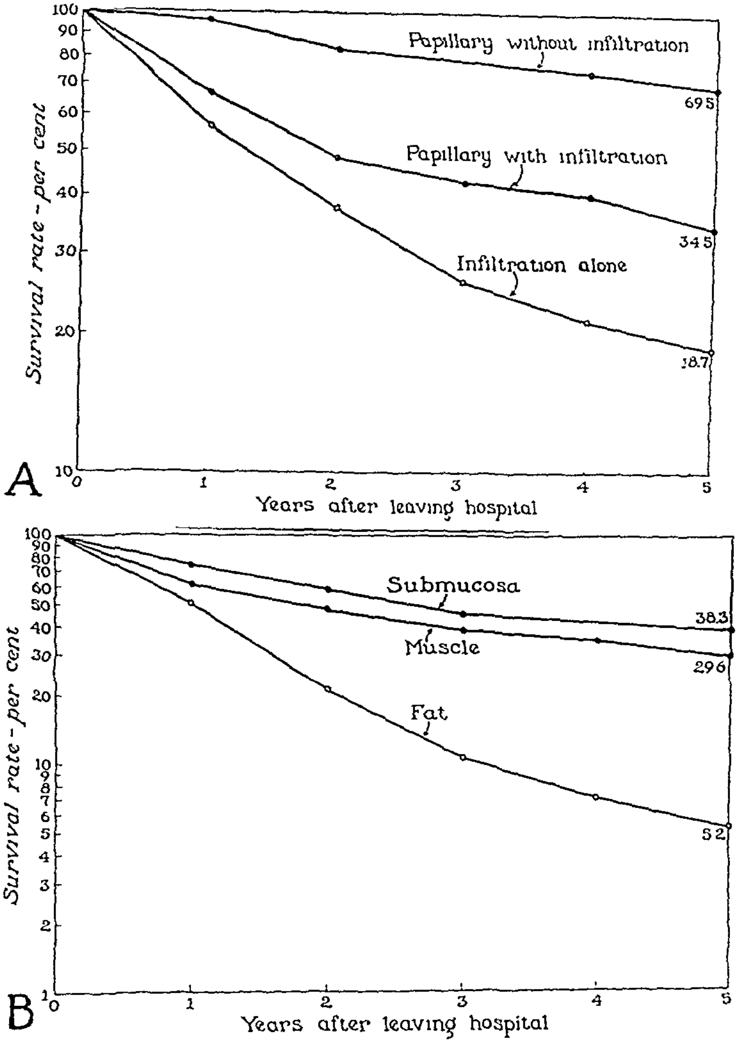

FIG. 6. *A*, Survival curves by type of infiltration in carcinoma of the urinary bladder. *B*, Survival curves by degree of infiltration in carcinoma of the urinary bladder.

Invasion of the vessels in the wall of the bladder. Involvement of vessels was seen in 102 of 274 cases. Two types of vascular invasion with tumor were seen: venous involvement and perineural lymphatic involvement. Our criterion for the demonstration of a vein was that it should have a definite coat of smooth muscle (fig. 8, *a* and *b*). In this way, artefacts could be avoided. Therefore, when venous invasion was noted the tumor cells were enclosed within a definite coat of muscle. Small lymphatics such as are found in the wall of the bladder are not identifiable as such in histologic preparations except for the knowledge that around the nerves there is a lymphatic sheath. Therefore, when lymphatic

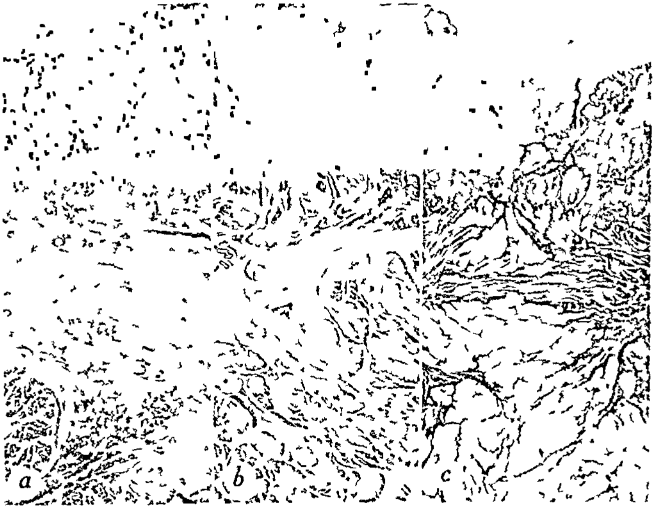

Fig. 7. Carcinoma of the urinary bladder showing various depths in bladder infiltrated with carcinoma. *a*, Nonpapillary transitional cell carcinoma which has invaded subepithelial connective tissue (submucosa). Invasion does not extend into the musculature (× 50). *b*, Papillary transitional cell carcinoma with beginning invasion of musculature (× 7). *c*, Mucoid adenocarcinoma with invasion of entire muscular coat of bladder and invasion of perivesical fat (× 4).

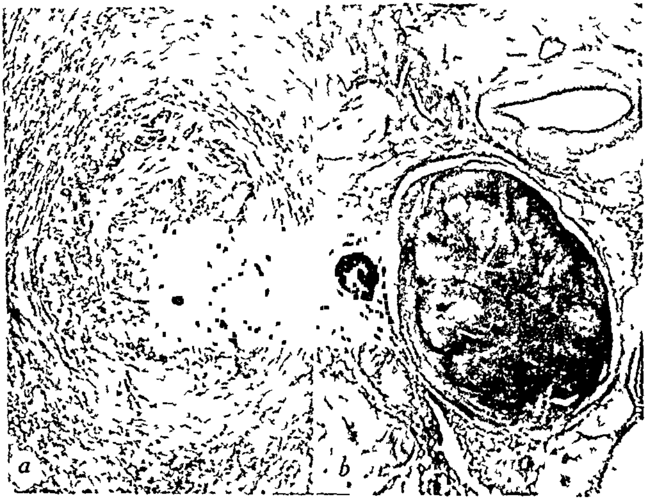

Fig. 8. *a*, Squamous cell carcinoma in a vein in wall of a bladder. Vein is situated in muscular layer (× 60). *b*, Carcinoma of the urinary bladder. A vein in perivesical fat is filled with tumor cells (× 18).

involvement was noted it was of the perineural type (fig. 9). Of the 102 cases in which vascular invasion occurred, venous invasion alone was noted in 23, perineural lymphatic involvement alone was seen in 64 and a combination of the two was observed in 15. The numbers of cases in which vascular invasion occurred in the various cytologic types of carcinoma are given in table 1. Invasion of vessels was rarely seen except where infiltrating tissue had penetrated to the deep muscular layer or perivesical fat, particularly the latter. This finding is consistent with the low survival rate for carcinoma of the urinary bladder which has involved the perivesical fat; when the perivesical fat has been infiltrated, the prognosis is very poor. The survival rate of our group of patients who had carcinoma of the urinary bladder without vessel involvement was 37.8 per cent. In those with vascular involvement the survival rate was 11.6 per cent. This demonstrated very graphically the influence of vascular invasion on the prognosis.

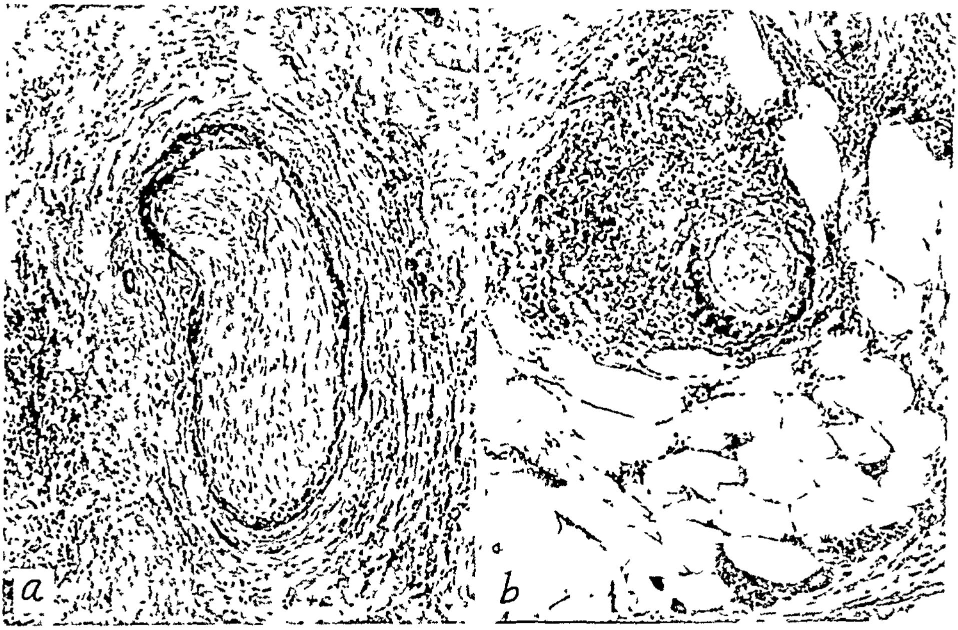

FIG. 9. *a*, Carcinoma of urinary bladder. Invasion of perineural lymphatics in wall of bladder (× 95). *b*, Carcinoma of urinary bladder. Invasion of perineural lymphatics. This nerve is situated in perivesical fat (× 115).

COMMENT

It is evident that several anatomic, morphologic and cytologic features are of importance in determining prognosis and treatment for patients who have carcinoma of the urinary bladder. It is important to know whether infiltration has or has not occurred. If infiltration has occurred, it is most significant to know whether the carcinoma has involved the perivesical fat or not. It would appear that groups A and B of Jewett might well be combined and labeled group A or some other arbitrary designation but that a second group consisting of cases in which invasion of the fat has occurred should be differentiated from the preceding group. This newly differentiated group might be labeled "group B." A second factor of importance is the classification of carcinoma into cell type. Transitional cell carcinoma offers a much better prognosis than squamous cell carcinoma or adenocarcinoma, whether found alone or mixed with either of the other two types. Of course, the bulk of the transitional cell epitheliomas are papillary in type, whether with or without infiltration. Another feature of importance in treatment and prognosis is the factor of involvement of vessels, which has a definite bearing on prognosis. Unfortunately, it is necessary to have adequate microscopic studies to determine the presence or absence of vascular invasion. It is impossible to determine invasion of the vessels as easily in the bladder as in the kidney because in the kidney there is, in the main, one renal vein, in the bladder there are many veins. The same holds true for nerves. In the kidney there is a concentration of nerves, in the bladder the converse is true. The importance of histologic grading of tumors of the bladder is accepted by many and, for this reason, the matter has not been discussed herein.

SUMMARY

From a histologic and anatomic study of 274 vesical tumors in which all or a portion of the urinary bladder along with the tumor had been removed surgically, certain features were determined to be of great importance in the matter of prognosis and treatment: first, whether invasion had or had not occurred, secondly, if the invasion had occurred, whether the fat was or was not involved, thirdly, whether evidence of invasion of the veins or lymphatics was present or absent, and fourthly, the cytologic and anatomic type of tumor, whether transitional cell, squamous cell or adenocarcinoma, or a mixture, and whether papillary or nonpapillary.

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CYSTITIS GLANDULARIS: A CONSIDERATION OF SYMPTOMS, DIAGNOSIS AND CLINICAL COURSE OF THE DISEASE

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Cystitis glandularis is of fairly uncommon occurrence and the difficulties encountered in the diagnosis of this lesion have been adequately described by various authors (Patch, Emmett and McDonald, Lowry, Hamm and Beard, etc.). Because of its often confusing cystoscopic and microscopic appearance, the condition may easily be mistaken for carcinoma and prolonged observation is necessary in some cases before the true nature of the lesion can be recognized. The correct differentiation of cystitis glandularis from bladder cancer is particularly important if one considers that recent advances in surgery have occasioned a more liberal employment of total cystectomy in the treatment of malignant neoplasm of the bladder.

In the following, an attempt will be made to present an outline of diagnosis, clinical course and prognosis of cystitis glandularis. Seven additional cases will be reported.

CASE REPORTS

Case 1. E. E. W., aged 52, a white male, case No. 40987, was admitted February 11, 1941. He complained of intermittent frequency and dysuria of 3 months' duration.

The physical examination was negative except for a healed fracture of the right hip. Blood count and blood chemistry were within normal limits and the Wassermann test was negative. The urine was fairly turbid, acid in reaction, contained a trace of albumin and isolated red and white blood cells. On culture, Streptococcus faecalis and Staphylococcus aureus hemolyticus were obtained.

Rectal examination revealed a moderately enlarged, somewhat indurated and boggy prostate. There was no residual urine and the bladder capacity was 250 cc.

Cystoscopic examination disclosed peculiar mammillated elevations involving vesical neck, trigone and lower posterior bladder wall. These lesions measured from 0.25 to 1 cm. in size and resembled bullous edema. While some of them were transparent, there were others which were more fleshy in character, suggesting possible tumor growth invading the bladder from the outside. It was noted that the more solid appearing lesions were particularly numerous in the region of the ureteral orifices. The remainder of the bladder was normal with a well defined borderline between diseased and normal bladder mucosa. Both kidneys functioned normally and pyelograms were essentially negative.

Biopsies taken repeatedly from various areas of the diseased bladder mucosa showed cystitis glandularis. Some thickening of the bladder epithelium which projected downward into the submucosa was noted. Isolated cell nests of stratified squamous epithelium occurring in small concentric masses were found in varying numbers in the submucosa Some of these glands were lined with tall columnar epithelium and mucus-producing cells

Treatment consisted of oral administration of urinary antiseptics followed by an inflammatory dose of deep x-ray therapy Response was prompt and on frequent follow-up visits, the patient remained asymptomatic, with the urine negative for albumin, blood and organisms Nevertheless, there was no significant change in the cystoscopic appearance of the bladder, which presented a striking discrepancy between the extensiveness of the bladder involvement and the apparent well-being of the patient When last seen 6 years and 10 months later (December 8, 1947), he continued in good health and had no urinary complaints Cystoscopy disclosed identical findings as at the time of admission, and the mucin test of the urine was strongly positive

Case 2 W M R , aged 57, a Negro, case No 10701, was admitted on January 8, 1941 with symptoms of frequency and dysuria of 1½ years' duration

Physical examination was entirely negative Blood count and chemistry were within normal limits The Wassermann test was negative The urine was slightly turbid, acid, contained a faint trace of albumin and a few red and white blood cells No growth was obtained on culture

The prostate was somewhat irregular, broader than normal and indurated in the midline, suggesting chronic prostatitis There was no residual urine The bladder capacity was 200 cc

Cystoscopic examination revealed almost identical changes as described in case 1 The vesical neck region, trigone, and lower posterior bladder wall were the site of the same type of mammillated proliferative lesions which varied from 0 25 to 1 cm in size As in the first case, there was a sharp line of demarcation between involved and apparently normal mucosa Studies of the upper urinary tract were essentially negative

Biopsies taken repeatedly disclosed cystitis glandularis with thickening of the surface epithelium which was ulcerated in some areas Numerous plugs and nests of epithelial cells were found in the submucosa Most of these nests were lined with tall columnar cells, some of which were of the mucus producing variety Following oral administration of urinary antiseptics, the symptoms subsided promptly, but there was no essential change in the appearance of the bladder while the patient remained under observation He was last cystoscoped 8 months after admission (September 12, 1941) Thereafter, the patient did not return, but it was learned that in 1942 he was admitted to another hospital where a diagnosis of multiple myeloma and multiple pathological fractures of the spine (D6, D12 and L2) was made During his stay at that hospital, no urological investigation was carried out because the patient had no urinary complaints He died of multiple myeloma on October 10, 1942 No autopsy was obtained

Case 3 A W B , aged 34, a white male, case No 53936, was admitted May 18, 1945 Six weeks prior to admission, the patient had painless hematuria of short duration Cystoscopy at that time revealed changes in the bladder, suggesting tumor growth and a biopsy taken from this area was interpreted as carcinoma

Physical examination was essentially negative except for moderate elevation of blood pressure. Blood count and chemistry were within normal limits. The Wassermann test was negative. The urine was slightly turbid, acid, contained no albumin, but numerous red and a few white blood cells were found. Urine cultures were negative.

The prostate was slightly enlarged and somewhat boggy. There was no residual urine and the bladder capacity was normal.

Cystoscopy revealed scattered over the trigone and particularly in the region of the ureteral orifices, papillary elevations from 0.25 to 0.5 cm. in size. Some of these lesions were pedunculated, others were sessile in character. The mucosa covering these elevations was thickened, edematous and pinkish in color, with no individual blood vessels visualized. The remainder of the bladder was normal.

Review of biopsies taken before and after admission revealed the typical picture of cystitis glandularis. Masses of glandular structures separated by strands of fibrous connective tissue were found in the submucosa. These glands varied in size and consisted mostly of stratified epithelium lined with tall columnar cells.

Examination of the upper urinary tract disclosed, as a coincidental finding, moderately advanced polycystic kidney disease with only slight impairment of kidney function.

The patient was treated with urinary antiseptics and an attempt was made at destroying the lesions by transurethral coagulation, but in spite of temporary regression, recurrences developed a few weeks later. Also, an inflammatory dose of deep x-ray therapy was of no avail. Nevertheless, the patient's general health continued good and he remained asymptomatic during the course of subsequent observation. When he was last examined, 2½ years after admission (November 10, 1947) there was no change in the cystoscopic and microscopic appearance of the lesions. Urinalysis was negative and no growth was obtained on culture.

Case 4. M. M. W., aged 70, a white female, case No. 27813, had been a patient of the Roswell Park Memorial Institute since February 17, 1937, following removal of the left breast for carcinoma. She was referred to the urological service on May 20, 1946 because of frequency, dysuria and hematuria of 2 weeks, duration.

Physical examination did not disclose any evidence of recurrent breast cancer. Blood count and chemistry were within normal limits. The Wassermann test was negative. The urine was turbid, alkaline, contained 1 plus albumin and numerous red and white blood cells. Cultures yielded growth of B. coli and B. aerogenes. The bladder capacity was 300 cc.

Cystoscopic examination disclosed ridges with fleshy pinkish-gray projections covering an area of approximately 4 cm. in the left lower posterior bladder wall. At first sight, these changes appeared consistent with invasion of the bladder wall by tumor growth from without, but on close inspection it gave the impression of resembling intestinal mucosa. Some bullous edema was noted in the adjacent portion of the mucosa. The remainder of the bladder was normal.

Study of the upper urinary tract did not reveal any abnormalities. On pelvic, as well as rectal palpation, some induration and fixation were felt in the left broad ligament area. On sigmoidoscopic examination, which was requested in order to exclude the possibility of a primary malignancy in the recto sigmoid area, a small polyp in the anterior wall of the midrectum was discovered. This was attached to a fixed base but histologic examination of the polyp did not disclose evidence of malignant degeneration.

Several biopsies from the bladder lesion revealed cystitis glandularis. Ulceration of the surface epithelium with marked inflammatory reaction was noted. In the submucosa, masses of epithelial cell nests were evenly distributed, together with mucus-producing glands showing many goblet cells.

The patient's urinary symptoms subsided promptly and did not recur following oral administration of urinary antiseptics. She has been followed for 17 months and when last examined on October 20, 1947, she was in good health. Cystoscopic, as well as rectal and vaginal examinations, revealed the same findings as on admission. The urine was negative. No growth was obtained on culture.

Case 5. E. D., aged 60, a white male, case No. 60153, was admitted on May 21, 1947 because of suspected carcinoma of the prostate. Thirty years prior to admission he had gonorrhea followed by urethral stricture, for which he had been treated intermittently. During the course of the disease he had repeated attacks of frequency, dysuria and occasional hematuria, and 1 year ago several bladder stones were removed suprapubically. Since then his urinary symptoms were relieved, but he noticed that a mucus-like sustance drained from the urethra following micturition.

The patient was a healthy looking male in good physical condition. Blood count and blood chemistry were not remarkable and the Wassermann test was negative.

The urine was cloudy and separated into two layers, namely, a thin mucoid layer on the surface and turbid urine underneath. The urine was acid, negative for albumin and sugar, and contained a moderate amount of leukocytes. The mucin test was strongly positive. On culture, B. coli was obtained.

Rectal examination revealed a moderately enlarged, indurated and irregular prostate, which felt like chronic prostatitis. The patient had 50 cc. of residual urine and it was noted that a considerable amount of mucus drained through the catheter, following evacuation of urine. The bladder capacity was 100 cc.

On cystoscopic examination, an opening to a bladder diverticulum was discovered in the left lower posterior bladder wall. Above and medial to this opening an area of granular thickening of the mucosa was noted, measuring 1.5 cm. in size. Other areas of similar appearance and size were found in the lower right posterior wall and in the dome of the bladder. These lesions were raised above the level of the mucosa and were surrounded in places by bullous edema. The remainder of the bladder showed chronic cystitis.

Examination of the upper urinary tract was not remarkable, and cystograms disclosed a walnut sized diverticulum.

Biopsies revealed cystitis glandularis. Ulceration of the surface epithelium and numerous glands of intestinal type were noted in the submucosa. These glands were composed largely of goblet cells causing the overall picture to closely resemble intestinal mucosa.

Treatment consisted of oral administration of urinary antiseptics. When last seen on October 10, 1946, there was no change in the patient's condition.

Case 6. G. W. S., aged 52, a white male, case No. 56681, was referred on April 17, 1946 because carcinoma of the bladder was suspected. The patient had frequency, dysuria and intermittent hematuria of 3 months' duration. Two months ago several bladder stones were removed by transurethral instrumentation. Upon admission, the patient had no symptoms referable to the genitourinary tract and he appeared to be in good physical condition.

Blood count and blood chemistry studies yielded normal values and the Wassermann test was negative.

The urine was clear, acid and contained a trace of albumin and scattered leukocytes. Staphylococcus aureus hemolyticus was identified on culture. The mucin test was positive.

Rectal examination revealed an essentially normal prostate, but there was fixation of the mid- and upper rectum due to induration in the perirectal space. There was no residual urine and the bladder capacity was 350 cc.

On cystoscopic examination, the trigone, vesical orifice and lower part of the posterior bladder wall were found to be the site of proliferative changes. These consisted of various sized ridges and folds, some of them assuming a polypoid appearance. The lesions were grayish-pink in color and fleshy in character. While they were generally homogenous in appearance, there were a few which showed individual blood vessels. The remainder of the bladder was normal.

Study of the upper urinary tract did not disclose any abnormalities. On proctoscopic examination, the rectal mucosa was normal up to the recto-sigmoid junction beyond which the instrument could not be passed due to fixation of the rectum to the perirectal tissues.

Biopsies from the bladder lesions disclosed cystitis glandularis. There were many irregular and tortuous glands lined with tall columnar epithelium and numerous goblet cells were noted. In other areas, epithelial cell nests were found in the submucosa which also showed evidence of inflammatory reaction.

Treatment consisted of administration of urinary antiseptics. The patient has remained under continuous observation and cystoscopic re-examinations have been carried out at approximately 3 month intervals. He remained in good health and when last seen on June 14, 1948, he was symptom-free. The urine was negative except for a positive mucin test. Rectal and cystoscopic examination disclosed almost identical findings as on first examination.

Case 7. F. H., aged 41, a white female, case No. 61516, was admitted October 24, 1947. Since 1945, she had intermittent pain in the right lower abdomen, which gradually increased in severity. For the past year, the pain was associated with frequency and dysuria, and for 6 months prior to admission, she had intermittent hematuria. Her general condition remained unimpaired.

Physical examination was essentially negative. Blood count and blood chemistry studies were normal and the Wassermann test was negative. Urinalysis, including culture, was negative.

Cystoscopic examination revealed a normal bladder capacity. In the region of the ureteral orifices, there were 2 areas, each 0.5 cm. in diameter, where the mucosa was thrown up into shallow ridges with isolated finger-like villi protruding. The lesions were grayish pink in color and no individual blood vessels could be distinguished. The remainder of the bladder was normal. No evidence of induration at the bladder base was noted on pelvic examination.

Study of the upper urinary tract did not reveal any abnormalities. Biopsies disclosed cystitis glandularis. There was thickening of the mucosa and two types of glands were encountered in the submucosa. One type consisted of stratified squamous epithelium, the innermost layer of which was composed of tall columnar cells. The other type was of the single layer variety, containing many mucous-producing cells.

The period of observation has been too short in this case to permit any comment on her progress.

DISCUSSION

Study of these 7 cases has suggested to us that cystitis glandularis should be considered a separate clinical entity. Its recognition may be difficult in some instances, yet there are certain findings which seem to be pathognomonic. In addition to a characteristic cystoscopic and microscopic appearance (figs. 1, 2, 3, 4, 5, 6, 7), there are other points of *diagnostic significance* which will be discussed in the following paragraphs.

It was observed that cystitis glandularis need not impair the patient's well-being to any great extent. Although cystoscopy revealed quite extensive lesions, and although the patients were suffering from a chronic condition with symptoms of varying severity and duration, it was noted that their general health remained unimpaired by the disease.

Another observation was that, as a rule, symptoms of the disease were not characteristic. Dysuria, always in combination with frequency, was the most common complaint (5 patients); intermittent hematuria (painful, 3 cases, painless, 1 case) was the next frequent symptom, and in one patient, the persistent elimination of clear and tenacious mucus was the only complaint. Since hematuria, frequency and dysuria are known to occur as a result of various urological disorders, not too much diagnostic significance can be attributed to their occurrence. It appears likely that they are caused by superimposed infection rather than by the disease itself. In contrast, constant elimination of clear mucus during and/or after urination is of diagnostic importance because it indicates the presence of mucus-producing glands in the genito-urinary tract (Emmett and McDonald). However, since mucin may be secreted in such small quantities that its elimination may occur unnoticed by the patient, it is advisable to carry out mucin tests whenever glandular cystitis is suspected.

The vesical neck region, trigone, as well as lower posterior and lower lateral walls, are the site of predilection, yet other parts of the bladder may occasionally be affected by the disease. *Interestingly enough, it was noted that the lesions* remained localized to the areas where they were originally observed, and neither progression nor regression took place throughout the period of observation. This is remarkable when one considers the prompt and apparently permanent abatement of symptoms following oral administration of urinary antiseptics. It follows that cystitis glandularis, although providing a fertile soil for superimposed infection, need not produce symptoms.

In regard to the portions of the genito-urinary tract involved, it is the consensus that cystitis glandularis is a condition which remains more or less confined to the bladder proper. Although isolated case reports indicate that certain types of epithelial cell nests have been found in the kidney pelvis and ureter (Everett and Wayburn), no evidence of upper urinary tract changes or impaired kidney function was determined in our series of cases, which is especially noteworthy if one considers that the ureteral orifices were often directly involved.

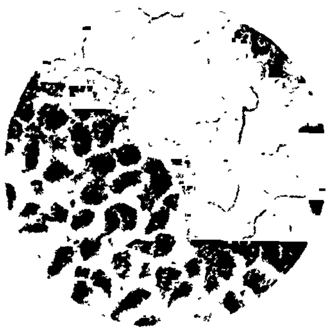

FIG. 1. Mammillated type, resembling tumor growth underneath mucosa

The absence of significant changes in the prostate and seminal vesicles as determined on rectal examination was also conspicuous. However, rectal or pelvic examination, respectively, may reveal fixation of the surrounding structures to the bladder, which was determined in 2 of our 7 cases.

In spite of the relative importance of the aforementioned factors, it must be understood that cystoscopic examination represents the most valuable procedure in the diagnosis of glandular cystitis. In carrying out cystoscopy, it was found remarkable that the bladder capacity was not significantly reduced and that examination was not unduly painful, although some of the lesions had assumed considerable proportions. In general, the cystoscopic picture of cystitis glandularis appears to be characterized by two distinctive types of lesions.

The first type consists of mammillated bleb-like structures which are separated by deep ridges (fig. 1). The areas involved are homogenous in character and no individual blood vessels can be distinguished. Although the lesion resembles bullous edema at first sight, it differs because the bleb-like elevations are fleshy in appearance and lack transparency. Co-existing bullous edema, adjacent to the areas of glandular cystitis, is a common finding.

The second type is characterized by the formation of fleshy villous-like proliferations (fig 2). In contrast to the first type, this lesion consists of islands which may be confluent or separated from each other by normal, or almost normal, bladder mucosa. Individual blood vessels are commonly observed, particularly where villi protrude into the bladder cavity.

While the first type may give the impression of tumor growth underneath the mucosa, the second may very easily be mistaken for tumor originating in the mucosa itself. However, it is characteristic for both forms that the transition from diseased to apparently unaffected bladder mucosa is usually quite abrupt.

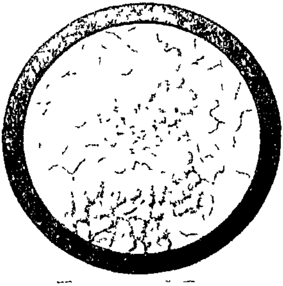

FIG. 2. Villous-like type, resembling primary bladder tumor

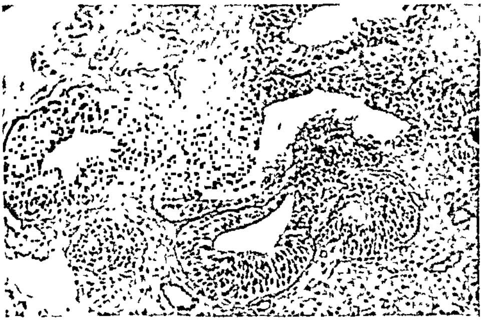

FIG. 3. Cystitis glandularis composed of stratified squamous epithelium

Although the aforementioned factors are of considerable diagnostic value, the final confirmation of the diagnosis of glandular cystitis rests with the histological findings. It has been emphasized by various workers (Emmett and McDonald, Lowry, Hamm and Beard, etc.), that the microscopic appearance of this condition may closely resemble either squamous cell or adenocarcinoma. Therefore, in order to avoid possible error close co-operation between the pathologist and urologist is essential.

The histopathological picture of cystitis glandularis is characterized by two types of lesions which occur in the submucosa either alone or in combination (figs. 3, 4, 5, 6).

The first and apparently more common type is comprised of glands of stratified squamous epithelium while the second type consists of glands formed by a single layer of cells. In the first instance the lumen is lined by columnar epithelium with occasional mucus-producing cells. In the second form, however, the presence of numerous goblet cells represents the outstanding feature. Here, the picture may resemble the microscopic appearance of the intestinal mucosa to such a degree that even the presence of Kultschitzky and Paneth cells has been reported (Ash and Friedman). By employing the muci-carmine stain, these

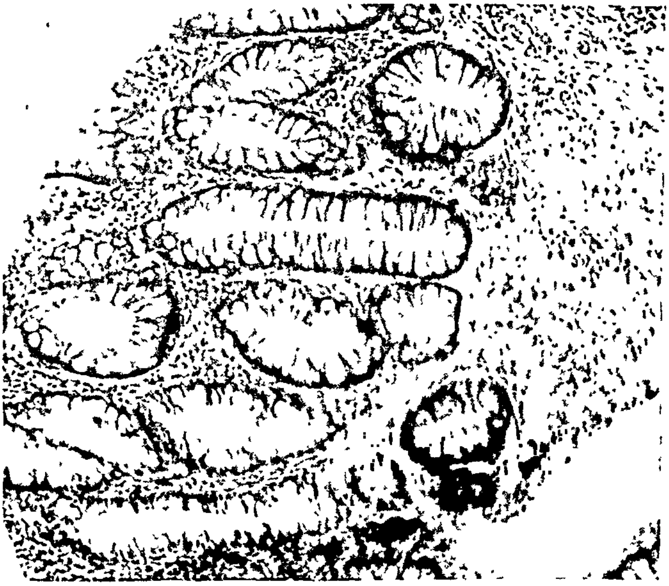

Fig. 4. Cystitis glandularis of intestinal type

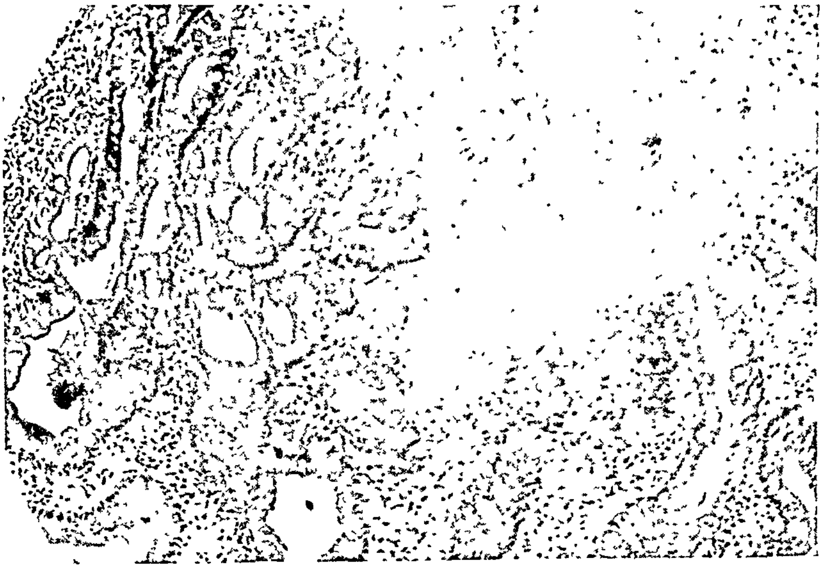

Fig. 5. Muci-carmine stain of glands of intestinal type in cystitis glandularis

mucus-producing cells can be identified by their bright red color and in doubtful cases its use is advocated as a valuable diagnostic adjunct.

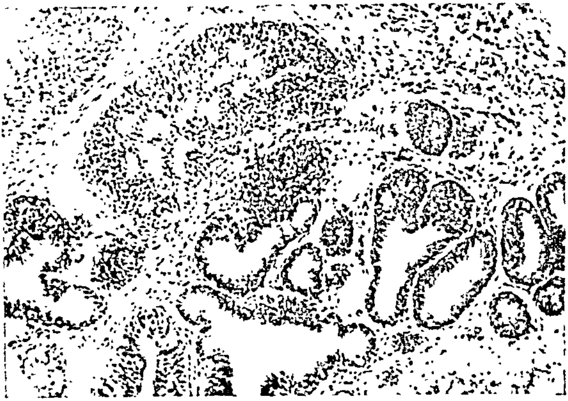

FIG. 6. Cystitis glandularis composed of stratified squamous and intestinal type of glands occurring in combination.

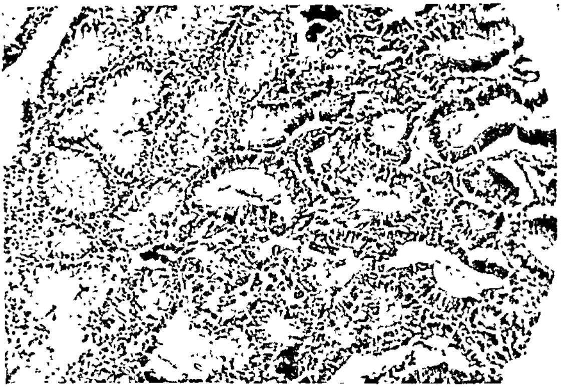

FIG. 7. Cystitis glandularis simulating adenocarcinoma. Subsequent cystectomy performed elsewhere refuted diagnosis of cancer, but disclosed cystitis glandularis.

It is evident that the changes described may be confused with carcinoma inasmuch as they indicate unusual activity of the epithelium. The interpretation of the histological picture may be further complicated if in some areas the glandular structures happen to be cut at a certain angle, thus simulating the appearance of adenocarcinoma (fig. 7).

However, the intact basement membrane of the glands, the regularity of the cells and the continued similarity of the findings on subsequent biopsies, in combination with clinical course and findings all refute the presence of a malignant lesion.

In correlating the histopathological findings with the cystoscopic appearance of the lesion, an interesting observation was made. When glands of the squamous cell type were present, the proliferative changes were predominantly edematous in character. On the other hand, intestinal type glands corresponded with lesions which had a more tumor-like aspect on cystoscopic examination.

A consideration of all the above factors demonstrates that the diagnosis of cystitis glandularis may be difficult at times. It must be differentiated not only from primary carcinoma of the bladder or prostate but also from malignant tumor invading the bladder from without (carcinoma of the rectum, of the pelvic organs, lymphoma and others). Inflammatory lesions in the perivesical space and foreign bodies entering the bladder from the outside must also be included in the diagnostic considerations.

No one symptom or finding, of and by itself, should be considered sufficient evidence for the establishment of the diagnosis. Recognition of this condition preferably should rest upon the proper evaluation of a combination of various signs and symptoms. The cystoscopic and histological findings occasionally, in combination with a positive mucin test in the urine, are the factors upon which an immediate diagnosis can be based. In doubtful cases, however, the lack of changes in the histological and cystoscopic appearance of the lesion will help to reveal the true nature of the condition. In these cases, prolonged observation with repeated biopsies is necessary before one is justified in rendering a final diagnosis of cystitis glandularis.

For prompt recognition of the disease it is of prime importance to be conscious of the existence of cystitis glandularis which in itself is of rather infrequent occurrence. By way of illustration, Emmett and McDonald reported an incidence of only 9 cases which they abstracted from the records of the Mayo Clinic; Foote collected no more than 3 cases from the material of the New York Hospital, and even the Army Institute of Pathology has but a few slides of glandular cystitis in their files. (Personal communication by Ash.) However, since our 7 cases were observed during a comparatively short period of time (3 of them within a year), the thought must be entertained that the incidence of this condition is more frequent that the literature would indicate. We are in agreement with Emmett and McDonald who state that many more cases of cystitis glandularis could be discovered if all biopsies from questionable bladder lesions were reviewed.

The pathogenesis of cystitis glandularis has been subject to discussion ever since its occurrence was first described by Stoerck and Zuckerkandl in 1899 and 1907. Its origin has been attributed by various authors either to metaplasia or dysontogenesis. The first view, which is primarily supported by Stoerck, Zuckerkandl, Patch and his associates, maintains that the lesion forms as the result of long standing irritation, such as occurs in chronic infection, the presence of stones, or the mechanical irritation in cases of exstrophy of the bladder The second opinion, which is upheld by Ash and Friedman, is based on the theory that these glandular structures arise from embryonal rests They believe that the "persistence of potentialities in specialized or undifferentiated vesical elements" is responsible for glandular cystitis

It is ultimately within the province of the pathologists to determine which of these theories represents the correct interpretation of the problem However, from a clinical point of view, there is one factor which should be regarded as significant Interestingly enough, a history of long standing or frequently recurring infection was elicited in only 2 of our 7 cases In the other 5, nothing was determined which could be interpreted as contributing to the development of glandular cystitis Thus, the thought presents itself that the disease may occur in some instances without a preceding stimulus, while in other cases, some irritant is required for the transformation of quiescent embryonal cell elements to the differentiated lesion (Ash and Friedman, Emmett and McDonald) Whether these glandular structures develop without an intermediate stage such as cystitis cystica, granularis or follicularis is subject to question In our series of cases, nothing was found to substantiate such a theory

Cystitis glandularis is a chronic disease which may remain stationary for an indefinite period of time Although the possibility of malignant degeneration has been mentioned by various authors (Patch, Foote, Ash, a o), no such evidence has been determined so far in our case series This observation gains in importance when one considers that 1 of our patients has been followed for over 6 years, 2 from 2 to 3 years, and 2 from 1 to 2 years

Nevertheless, despite the fact that the lesions in these cases did not disclose perceptible changes in their cystoscopic and microscopic appearance, the possibility of carcinomatous degeneration always must be entertained Therefore, in order to be on the alert for such a complication, cystoscopic examination and biopsy repeated at 4 to 6 month intervals are indicated In the interpretation of these biopsies, the often deceiving picture simulating carcinoma must be remembered in order to avoid errors of far-reaching consequence

Treatment of cystitis glandularis should be conservative Active bleeding from a small area can be arrested by transurethral coagulation If infection is present, its source, if determined, should be eliminated In the other cases, the infection should be treated with urinary antiseptics Destruction of the proliferative changes by means of coagulation either through the cystoscope or through the open bladder has been advocated and may yield permanent results in small lesions involving only limited areas of the bladder However, when numerous portions of the bladder and particularly the region of the ureteral orifices are involved, it appears doubtful whether satisfactory response can be obtained In patients who are asymptomatic, with negative urine, watchful waiting seems to be the wisest course

SUMMARY

It is suggested that cystitis glandularis, although uncommon, may occur more often than is indicated from the study of the literature

However, the intact basement membrane of the glands, the regularity of the cells and the continued similarity of the findings on subsequent biopsies, in combination with clinical course and findings all refute the presence of a malignant lesion.

In correlating the histopathological findings with the cystoscopic appearance of the lesion, an interesting observation was made. When glands of the squamous cell type were present, the proliferative changes were predominantly edematous in character. On the other hand, intestinal type glands corresponded with lesions which had a more tumor-like aspect on cystoscopic examination.

A consideration of all the above factors demonstrates that the diagnosis of cystitis glandularis may be difficult at times. It must be differentiated not only from primary carcinoma of the bladder or prostate but also from malignant tumor invading the bladder from without (carcinoma of the rectum, of the pelvic organs, lymphoma and others). Inflammatory lesions in the perivesical space and foreign bodies entering the bladder from the outside must also be included in the diagnostic considerations.

No one symptom or finding, of and by itself, should be considered sufficient evidence for the establishment of the diagnosis. Recognition of this condition preferably should rest upon the proper evaluation of a combination of various signs and symptoms. The cystoscopic and histological findings occasionally, in combination with a positive mucin test in the urine, are the factors upon which an immediate diagnosis can be based. In doubtful cases, however, the lack of changes in the histological and cystoscopic appearance of the lesion will help to reveal the true nature of the condition. In these cases, prolonged observation with repeated biopsies is necessary before one is justified in rendering a final diagnosis of cystitis glandularis.

For prompt recognition of the disease it is of prime importance to be conscious of the existence of cystitis glandularis which in itself is of rather infrequent occurrence. By way of illustration, Emmett and McDonald reported an incidence of only 9 cases which they abstracted from the records of the Mayo Clinic; Foote collected no more than 3 cases from the material of the New York Hospital, and even the Army Institute of Pathology has but a few slides of glandular cystitis in their files. (Personal communication by Ash.) However, since our 7 cases were observed during a comparatively short period of time (3 of them within a year), the thought must be entertained that the incidence of this condition is more frequent that the literature would indicate. We are in agreement with Emmett and McDonald who state that many more cases of cystitis glandularis could be discovered if all biopsies from questionable bladder lesions were reviewed.

The pathogenesis of cystitis glandularis has been subject to discussion ever since its occurrence was first described by Stoerck and Zuckerkandl in 1899 and 1907. Its origin has been attributed by various authors either to metaplasia or dysontogenesis. The first view, which is primarily supported by Stoerck, Zuckerkandl, Patch and his associates, maintains that the lesion forms as the result of long standing irritation, such as occurs in chronic infection, the pres-

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POLYMORPHOUS CELL SARCOMA OF THE BLADDER. CASE REPORT[1]

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Recent literature has adequately dealt with the general subject of sarcoma of the urinary bladder.[2] Such tumors are relatively rare, only 151 having been reported to 1943.[3]

Since 1943, as far as we were able to determine, there have been 5 additional cases of sarcoma of the bladder reported. A case of rhabdomyosarcoma,[4] a fibromyxosarcoma,[5] a primary osteogenic sarcoma,[6] a leiomyosarcoma,[7] a lymphosarcoma.[8] This brings the total number of the cases reported to date to 156.

CASE REPORT

A white widow, aged 57, was admitted to Huron Road Hospital, East Cleveland, October 25, 1946. Her chief complaint was hematuria, associated with frequency, tenesmus, and dysuria. A provisional diagnosis of tumor of the bladder was made. The family and past histories were irrelevant.

The patient's urinary complaints dated from September 1945, when she consulted her physician for vulvar itch. She had no treatment until May 28, 1946, when hematuria made its appearance. At the time a local examination revealed a growth in the region of the external urinary meatus. It was described as being red and having the appearance of granulation tissue. Her physician made a diagnosis of urethral caruncle and removed the growth June 15, 1946. The gross specimen consisted of several masses of tissue, each approximately 2 cm in length and 5 mm in diameter. The tissue was pale gray, fleshy and compressible. Examination of microscopic sections showed a mass of tissue partially covered by a thin layer of stratified squamous epithelium and in some areas showing transitional columnar epithelium. Beneath the epithelium there were large masses of closely packed large round cells, numerous lymphocytes, in some places surrounding blood vessels. In other areas, these cells formed large solid sheets with no evidence of invasion. The final diagnosis was urethral caruncle.

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[1] Read at annual meeting, North Central Section, American Urological Association, Cleveland O, October 23-25 1947

[2] Ley, M and Bell, W L J Urol, 57: 251-256, 1947

[3] Crane, A R and Tremblay R G Ann Surg 118 887-908, 1943

[4] Khoury E N and Speer, F D J Urol, 51: 505-516 1944

[5] Tahara G Burt, K L and Hess F Urol & Cut in Rev 49: 534-538, 1945

[6] Tremblay, R G, Crane, A R and Harris A J Urol 51: 143-148, 1944

[7] Rathbun, N P and Wehrbein, H L J Urol, 51: 31-36, 1944

[8] Smith G and Kellert, L Urol & Cut in Rev, 48: 564-566, 1944

The patient left the hospital on the second postoperative day, the growth having been removed by sharp dissection and healing effected per primam. There were no other physical or laboratory findings or, particularly, genito-urinary findings of note, although no urological examination was made.

The patient returned October 26, 1946. During the month immediately preceeding admission she had had frequency of urination accompanied by tenesmus and dysuria. On one occasion, a few days before admission, there had been considerable hematuria. She complained that her urine had become thick and that walking caused a "jarring distress" in her lower abdomen, possibly the result of residual urine.

Physical examination was negative, except for the pelvic findings, which will be described.

Cystoscopy disclosed a bladder capacity in excess of 32 ounces. The bladder mucosa was atrophic. A lobulated tumor of considerable proportions was seen to encroach in all directions in the area of the vesical sphincter. The ureteral orifices could not be visualized, hence there was no upper urinary tract pyelographic investigation. Indigo carmine tests were only partially satisfactory. The dye could be seen in the circulating fluid in normal time. A McCarthy resectoscope was substituted and a considerable amount of tumor tissue was removed 1) to reduce the element of obstruction and 2) to obtain biopsy specimens.

Taking advantage of the spinal anesthesia, a complete pelvic examination was done. This revealed an extension of the pathological process laterally. The tumor mass in the bladder appeared to have already extended beyond that organ, especially on the right side. The ovaries were situated high in the pelvis, round, fibrotic and not involved in the tumor mass. The uterus seemed fairly fixed. The atonic bladder, when fully distended, rose high out of the pelvis to a position well above the umbilicus. However, thorough examination by a competent neurologist failed to reveal responsible nervous system disease.

From the first x-rays it seemed that the case was one of probable cord bladder. On October 28, 1946 additional x-rays, cystograms and intravenous pyelograms were taken to show the presence of a tumor mass in the floor of the bladder, clinically described. The tumor could not be well visualized, but the floor of the bladder was seen to be elevated above the level of the symphysis pubis for a distance of about 2 cm. by a soft tissue structure, the density of which was definitely increased above that of the remaining structures in the pelvis minor. This crescent shaped object lying between the symphysis and the lower border of the bladder was about 5 by 2 cm. in size. Whether this represented the clinically visualized tumor in the floor of the bladder could not be definitely determined. The kidney calyces, pelves and ureters were normal in size, configuration and position. There was no hydronephrosis, nephroptosis or calculus. The visible bones were normal in appearance.

The biopsy consisted of 8 masses of grayish white and compressible tissue, the largest measuring 7 mm. in diameter. Microscopic examination showed several small tumor masses from the bladder covered by a thin layer of stratified squamous epithelium with considerable desquamation of the surface portion. Beneath the epithelium there were masses of tumor tissue consisting of closely packed masses of polyhedral cells, lying within a loose vascular stroma. The tumor cells varied in size, for the most part medium and large. A few multinucleated cells were present. The nuclei were large, vesicular and an occasional mitotic figure was seen. The final diagnosis was polymorphous cell sarcoma of the bladder (fig. 1).

Examination of the blood revealed moderate anemia, no leucocytosis and negative serology. The urine contained many leucocytes and erythrocytes, and on culture, B. coli. Spinal fluid was negative.

Deep x-ray therapy was given, a total of 900 r. units in each of 3 fields.

The patient showed marked improvement. The follow-up care consisted of bladder hygiene, antispasmodics and general sedation. The residual urine at one time reached 2 ounces. Repeated pelvic examinations showed a rapid diminution in the masses. An examination in the office 6 weeks after completion of the deep x-ray therapy revealed no evidence of the tumor, and the uterus was freely movable.

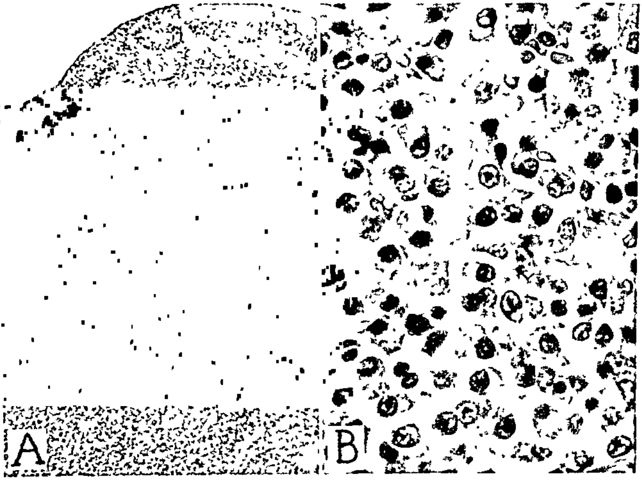

FIG. 1

The patient was re-admitted to the hospital on February 7, 1947. Cystoscopy showed several areas of pale white scarring on the bladder mucosa with ragged surface desquamation. The ureters were stenosed. All efforts to pass catheters were unsuccessful. Indigo carmine appeared in 3 plus concentration in 14 minutes from both sides. It was thought that the indolent areas might still respond to silver nitrate therapy or superficial fulguration.

Bilateral retrograde pyelograms showed good visualization of the left ureter and partial visualization of the middle and inferior calyces of the left kidney. The visualized structures were normal in appearance and position. The upper calyx of the left kidney was not visualized. An attempted right retrograde pyelogram was unsuccessful, and no dye could be seen in the right urinary tract. A small amount of dye collected around the distal end of the right ureter at the end of the engaging tip catheter. The visible bones were normal in appearance.

On March 25, 1947, the patient suffered a simple fracture of the neck of the right femur. A Smith-Peterson nail was inserted on April 2, 1947 by one of us (H. W. B). X-rays showed the pin and fracture to be in good alignment. This was not a pathological fracture, as otherwise the bony structures were quite normal. The patient was up in a walker on April 11, 1947, and progressed rapidly, so far as the orthopedic condition was concerned.

On April 23, 1947 two sets of pyelograms showed no deformity. The hypotonic type of neurogenic bladder was again present. The residual urine was approximately 17 ounces and there was an almost total lack of sensibility to pain. Cystoscopy was done without anesthesia. No evidence of tumor was found but the gray, geographic patches on the mucosa were still present. Some of these, removed for microscopic examination, showed only necrotic material. Cultures of the bladder urine showed B. pyocaneus and B. coli.

On September 3, 1947 the patient was readmitted to the hospital for cystoscopy, retrograde pyeloureterograms and pelvic examination under spinal anesthesia. The patient was instructed to void immediately before getting on the table. The residual urine was approximately 17 ounces. It was hazy and the last urine to flow from the scope presented considerable purulent debris. This examination revealed no recurrence of the tumor.

The biopsy slides of the caruncle were reviewed. More exhaustive examination found them to very closely resemble the tumor. It was thought that the possiblitiy of sarcoma should have been considered for the caruncle.

SUMMARY

Clinicians have acknowledged the high sensitivity of lymphosarcoma. Still there are marked individual differences of the lymphoma group, differences not demonstrably related to structure. Certainly in the case being reported we have a tumor of extreme radio-sensitivity. The tumor cells literally melted away as a result of deep x-ray therapy. Obviously, one cannot be assured that this is a cure. A periodic recheck of the tumor area will be necessary. Radio-sensitivity does not mean the certainty of cure by irradiation nor does radio-resistance imply that a given tumor is not curable by irradiation. Radio-sensitivity seems to increase with the embryonal quality of the tumor cells, and the increasing degree of anaplasia.

We must remember too, that in the case of the extremely sensitive tumors, the radiologist is apt to be so impressed with the initial regression of the disease that he fails to push his treatment to tolerance. He waits until after a period of quiescence, the disease recurs in a more resistant form, and then he must essay to do, under poorer conditions, what he failed to do at the start.[9]

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[9] Stewart and Farrow: In Treatment of Cancer and Allied Diseases. New York: Paul B. Hoeber, Inc., 1940, vol. 1, chapt. 8.

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TRANSURETHRAL RESECTION OF THE VESICAL NECK IN INFANTS AND CHILDREN[1]

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Urinary stasis, the cause of which is below the level of the ureteropelvic junction, continues to be one of the most difficult problems in pediatric urology. All too often the etiology and pathogenesis of the condition is obscure so that the therapeutic problem is poorly defined. Even when the causative factor is clear-cut, therapeusis may be most difficult to carry out.

Numerous diagnoses have been applied to this group of cases, among which are: congenital atony of the urinary tract, neurogenic dysfunction of the pelvis, ureters and bladder, congenital absence of the muscular coverings of the urinary tract and obstructive uropathies with the site of obstruction at such places as the ureter, ureterovesical junction, vesical neck, urethra and urethral meatus. As time goes on more and more cases seem to fall into the classification of obstructive uropathies, so much so that one wonders if all could be so diagnosed if our knowledge were more complete. One is confronted however, with such situations as unilateral ureteropyelectasis with a dilated ureteral orifice and reflux, in which the opposite kidney and ureter are normal and no vesical dysfunction can be elicited. It is difficult to ascribe such a condition to obstruction.

As we review progress in this field, we cannot forget that less than two decades ago many cases of urinary retention confined to the bladder were called "congenital atony" or "neurogenic dysfunction." We now know that nearly all of these were unrecognized obstruction at the vesical neck. Also we now know that in almost every case in which a bona fide lesion of the central nervous system affects the bladder, the resulting dysfunction is one of increase rather than decrease of vesical tonicity. The pathogenic disturbance in such cases is of course at the vesical neck. Apropos of this experience one wonders if we are failing to recognize abnormal conditions at the ureterovesical junction which may cause similar dysfunction and stasis. Are we yet unable to recognize physiologic obstruction at the ureterovesical junction—or better, how to correct it?

Barring a few well-defined and rather rare obstructive conditions which occur at the ureterovesical junction, such as ureterocele and congenital stenosis, successful therapeutic efforts to correct urinary stasis (below the level of the ureteral pelvic junction) have been directed toward infravesical conditions (affecting the vesical neck, prostate and urethra). It is concerning this type of therapy that this study has been made.

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[1] Read at annual meeting, North Central Section, American Urological Association, Cleveland, O., October 24, 1947.

MATERIAL FOR STUDY

We have selected for this study all patients at the Mayo Clinic less than twenty years of age on whom transurethral operation has been done for abnormal conditions at the vesical neck or in the prostatic urethra, from October 1, 1941, through December 31, 1946. This did not include 5 patients in this age group who underwent resection because of a neurogenic bladder caused by transverse myelitis of traumatic, inflammatory or neoplastic origin. It was found that there were 49 cases which would fall into this classification for this period of slightly more than 5 years. The study was begun with October 1941, because Thompson has previously reported the cases at the clinic up to that time; the report comprised 63 cases, in 48 of which transurethral operation was performed. Our present study therefore concerns 49 patients, of whom 34 were male and 15 female. By means of re-examination of patients and follow-up letters, we have recent data concerning the condition of 40 of the 49 patients. For the remaining 9 we have used the record of the patient at the time of dismissal in evaluating the result of operation.

TABLE 1. *Age and sex of patients, group I (myelodysplasia)*

AGE	MALE	FEMALE
yr.		
Less than 10	5	4
10–15	2	2
More than 15	2	3
Total................	9	9

The 49 cases under discussion have been divided into two groups: (1) vesical dysfunction resulting from myelodysplasia and spina bifida, and (2) congenital obstruction of the vesical neck. It might seem that such a division would be difficult to make accurately. On review of the cases, however, the segregation was not difficult. The patients in the myelodysplasia group have many or all of the typical findings of spina bifida, including vesical and rectal incontinence, sensory and motor changes, club feet, and so forth. It could be argued that an occasional patient in the second group might be suffering from minor changes due to a spina bifida which could not be demonstrated. Although this could be true, the character and findings of the two groups being so well defined would suggest that such confusion should occur only rarely.

GROUP I. VESICAL DYSFUNCTION RESULTING FROM MYELODYSPLASIA AND SPINA BIFIDA

Age and sex. There were 18 patients in this group. Nine were male and 9 female. Their ages varied from 3 to 18 years (table 1).

Symptoms. The presenting symptom of all the patients in this group was varying degrees of urinary incontinence associated with a poor urinary stream. In nearly all cases there were also varying degrees of rectal incontinence, although in many this could be handled fairly well with a regular regimen of enemas.

Findings. Renal function in this group was much better than in the second group of congenital obstruction of the vesical neck. The concentration of urea was less than 40 mg. per 100 cc of blood in 16 of the 18 cases. In the remaining 2 cases the values were 50 and 94 mg. per 100 cc, respectively. Fourteen of the 18 patients were studied by excretory urography. The condition of the upper part of the urinary tract as determined by excretory urography is shown in table 2.

Urinalysis showed 13 of the 18 patients to have infected urine, while the urine of the other patients was clear.

TABLE 2. *Condition of kidneys and ureters as determined by excretory urography, group I (myelodysplasia)*

	MALE	FEMALE
Excretory urogra 1 not done . . .	0	4
Normal kidneys and ureters .	6	2
Evidence of pyelo-ureterectasis	2	3
Congenital anomaly	1	0
Total	9	9

TABLE 3 *Amount of residual urine, group I (myelodysplasia)*

AMOUNT	MALE	FEMALE
cc.		
None	1	0
Less than 60	0	3
60–100	2	0
More than 100	6	6
Total . . .	9	9

Residual urine determination is of interest as shown in table 3. The presence of residual urine in most cases signifies that almost all have some degree of obstruction of the vesical neck.

Cystoscopy revealed trabeculation of the bladder in all cases. In some of the male patients a definite spasticity or contraction of the vesical neck characteristic of most cord bladders could be seen.

Operation. Transurethral resection of the vesical neck was carried out in all cases. In 1 male patient the resectoscope was introduced through an external urethrotomy incision in the bulbous urethra (as suggested by Nesbit) to avoid trauma to a small pendulous urethra. In the infants and children the small 18 F. cold knife punch was used. In the older patients with larger urethras the 24 F. or 27 F. cold punch was used. In all cases tissue was excised from the entire circumference of the vesical neck. In the male patients, resection was carried out to the verumontanum as is done in our ordinary transurethral prostatic resection. In all cases the resection was carried as widely as possible. After operation, a urethral catheter was left indwelling for from 48 to 72 hours.

In 2 female patients, in addition to the transurethral resection an attempt was made to strengthen the external urethral sphincter by means of a "Kelly" operation on the urethra.

Results. The operative results are listed in table 4.

It can be seen from table 4 that the operative results in this group of cases are far from satisfactory. Only one in 3 patients is completely relieved of symptoms. It will be noticed that the results were better in the female than the male patients. This is probably due to the fact that in women we do have a crude method of increasing the "urethral resistance" or tonicity of the external urethral sphincter by such procedures as the Kelly or Kennedy plastic operation on the urethra.

Comment. It is our opinion that the problem of vesical dysfunction in patients with myelodysplasia is composed of two parts. The first part is the typical "cord" bladder, with increased detrusor tone and trabeculation, and spasticity, contraction or "dysectasia" of the vesical neck or so-called internal sphincter. This condition is similar to that found in patients with transverse myelitis resulting from acquired lesions of the cord. The second part is a weakness and lack of tone of the external urethral sphincter. This condition is found almost exclusively in patients with congenital myelodysplasia and is apparently the reason why incontinence persists in spite of the fact that residual urine has been eliminated by transurethral resection. It is fortunate that this situation does not occur commonly in cord bladders resulting from acquired lesions of the cord; otherwise transurethral resection would not be able to re-establish normal vesical function in such a high percentage of cases as it does.

TABLE 4. *Results of transurethral operation, group I (myelodysplasia)*

	MALE	FEMALE
Good: Voids freely, no residual urine, no incontinence	2	4
Improved: No residual urine, no incontinence, but stream not free	1	0
Improved: Voids freely, no residual urine, but some degree of incontinence persists	4	3
Improved: Normal vesical function established but patient died in uremia a few months later	0	1
Unimproved	2	1
Total	9	9

The therapeutic problem in myelodysplasia, therefore, is a dual one: first, to relieve the urinary obstruction, eliminate the residual urine and establish a free urinary stream, and second, to establish urinary continence. The first can be readily accomplished by means of adequate transurethral resection. The second has not been solved adequately. In the female patients who are old enough (in their teens), urethral resistance and tonicity of the external sphincter can be improved in some cases with muscle-imbricating operations such as the Kelly and Kennedy operations. This treatment has proved successful in our experience in 2 cases, one of which is abstracted in the succeeding paragraphs. So far, the problem has not been successfully attacked in the male. Cases illustrating the problem may be of interest.

Case 1. A girl, aged 17 years, came to the clinic in September, 1945. She had been well until 1940, at which time an operation had been performed for spina bifida cystica. The patient had had no disability from this condition, but operation had been advised to avoid future trouble. After the operation, urinary retention developed and was followed later by vesical and rectal incontinence. Areas of complete anesthesia had developed in the saddle area and on the posterior aspect of the right thigh, and complete anesthesia had occurred below the right knee. This had resulted in a decubitus ulcer on the right heel, which had exposed the os calcis and had produced extensive osteomyelitis. An extensive decubitus ulcer had developed on the right buttock and had exposed the ischial tuberosity.

As regards urologic findings, the patient was continually wet. Small spurts of urine would issue from the urethra every 3 to 8 minutes. On several occasions, less than 30 cc of residual urine was found in the bladder although on one occasion 60 cc was obtained. Cystoscopy revealed that the bladder was moderately trabeculated and of large capacity. Because of the small amount of residual urine, it was felt that transurethral resection of the vesical neck would be of little help. We wondered, however, if the tone of the external sphincter could be improved with a muscle-plicating type of operation, such as the Kelly operation, on the urethra. It was decided to try both procedures.

On October 22, 1945, transurethral resection was performed, and a total of 3 gm. of tissue was removed from the entire circumference of the vesical neck. After the operation the vesical function was not changed except that the small amount of residual urine had been eliminated. The urine still was expelled from the bladder in small spurts every 3 to 8 minutes. A Kelly operation on the urethra was then performed. After removal of the catheter, the patient was able to void every 2 hours and remained dry. If awakened once at night to void, she did not wet the bed. She was able to empty the bladder completely. When the latest information about this patient was obtained, 16 months after the operation had been performed, the vesical function was still normal and the urine clear. She could initiate micturition at will.

After the urologic treatment the patient's right leg was amputated below the knee and a decubitus ulcer on the right buttock was excised. Both wounds healed well and have remained healed. The patient walks well on her artificial limb and, despite the fact that the stump is anesthetic, she has as yet had no trouble with trophic ulcers.

Case 2. A boy, aged 11 years, was admitted to the clinic on August 13, 1946, with the complaint that he "couldn't hold his urine." The parents stated that when the boy was 6 weeks of age, a "lump" on his spinal column had been removed surgically. Since that time he had been in good health except for "total" urinary incontinence and "partial" fecal incontinence. There was no history of chills and fever although the parents stated that the boy had frequent "chilly sensations." They stated that he had never passed a urinary stream, but rather suffered from an almost constant dribbling of urine.

Examination showed the scar over the upper sacral area and the typical findings of myelodysplasia. The patient's temperature was 99.2° F. The penis and foreskin were edematous and excoriated from being constantly wet with ammoniacal urine. During the examination fecal material was passed and there was constant dribbling of urine.

The patient was hospitalized and a determination of residual urine was made which showed 250 cc of foul, ammoniacal urine to be present. Culture showed the infecting organism to be Escherichia coli. An excretory urogram revealed bilateral pyelo-ureterectasis, grade 2+ (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition), with moderate reduction of function. A retrograde cystogram showed reflux up the dilated right ureter. None was observed on the left. The concentration of urea was 36 mg. per 100 cc of blood. The results of studies on the blood were within normal limits. After catheterization the temperature rose to 104° F. and remained elevated for 5 days. The patient was treated by means of an indwelling catheter, intravenously administered fluids, penicillin and sulfathiazole.

Transurethral resection was done on August 22, 1946. The 18 F. cold knife punch passed easily through the urethra. The bladder was trabeculated grade 2+. There was a definite collar of tissue around the vesical neck. Numerous pieces, weighing a total of 2 gm., were removed from the entire circumference of the prostatic urethra. On microscopic examination the tissue removed was reported to be "inflammatory muscle." There was no postoperative febrile reaction.

After operation the patient was able to void a normal, forceful urinary stream and empty his bladder completely. The urinary control was not perfect, however. When the bladder filled to about 100 cc some leakage occurred. If he voided before this much urine accumulated in the bladder he stayed dry. The patient was given a small penile incontinence clip by means of which he can keep dry without too frequent trips to the toilet. He is able to stop and start his urinary stream at will during micturition.

GROUP II. VESICAL DYSFUNCTION RESULTING FROM CONGENITAL OBSTRUCTION OF THE VESICAL NECK

There were 31 patients in this group. The examination of these patients demonstrated nothing that would suggest a neurologic lesion such as spina bifida and myelodysplasia, although it must be admitted that such a lesion in mild form could conceivably be present in an occasional case in this group even though there were no clinical or roentgenographic findings suggesting it. The marked difference in response of this group to treatment suggests that myelodysplasia was not a factor of importance.

Age and sex. Of the 31 patients in this group 25 were male and 6 were female. Ages of patients ranged from 1½ to 19 years as noted in table 5.

TABLE 5. *Age and sex of patients, group II (congenital obstruction of vesical neck)*

AGE	MALE	FEMALE
yr.		
Less than 2	2	0
2–4	4	0
5–7	5	3
8–9	6	3
10–11	3	0
12–14	1	0
15–19	4	0
Total................	25	6

TABLE 6. *Symptoms complained of by thirty-one patients less than twenty years of age suffering from congenital obstruction of the vesical neck (group II)**

CONDITION	MALE	FEMALE	TOTAL
Nocturnal enuresis or diurnal incontinence or both..	12	2	14
Recurring chills and fever or recurring infection..	7	6	13
Frequency or urgency or both........	7	2	9
Symptoms of obstruction: poor stream; strains to void, and so forth...........................	8	1	9
Dysuria.......	5	1	6
Attacks of complete retention..................	4	0	4
Vomiting	3	0	3
Renal pain...	2	1	3
Recurrent cloudy urine........................	2	1	3
Convulsive seizures..............................	2	0	2
Nocturia	2	0	2
No symptoms: pyuria discovered on routine examination	2	0	2
Distended abdomen..............................	2	0	2
Anorexia..	1	0	1
Recurring abdominal pain........................	1	0	1
Hematuria initial, chief symptom...............	1	0	1
Hematuria *only* symptom........................	1	0	1
Craves water.....	1	0	1

* Figures indicate the approximate number of times each symptom was complained of by the patients in the series.

Symptoms. It is interesting to review the symptoms complained of by these 31 patients (table 6).

It will be noticed that although enuresis and incontinence heads the list, it is by no means as common as in patients with myelodysplasia. Furthermore, the "incontinence" in most cases was an overflow, most commonly occurring at night.

Recurring chills and fever are common symptoms, and when encountered in children demand investigation of the urinary tract. Vesical symptoms such as dysuria, frequency, urgency and obstructive symptoms such as a poor, interrupted stream apparently occur in less than a third of these patients. This means that the absence of vesical symptoms should not lull the physician into disregarding the urinary tract as the possible source of trouble. This point has been emphasized repeatedly by one of us (H. F. H.).

The more unusual symptoms such as anorexia, vomiting, convulsive seizures and polydypsia are important because so often vesical symptoms are absent in such cases. They are of course the warning signs of uremia or impending uremia and all too often are misinterpreted. A urinalysis should be done in the case of every sick child, and if pyuria is present urinary stasis must be considered and excluded as the source of the patient's illness. Rarely, one encounters a case of urinary stasis in which the patient is a child with advanced pyelo-ureterectasis, urinary retention and uremia but the urine is microscopically negative. Such a case is the exception that proves the rule.

TABLE 7. *Values for blood urea, group II (congenital obstruction of the vesical neck)*

PREOPERATIVE BLOOD UREA	MALE	FEMALE
mg. per 100 cc		
Less than 50	15	4
50–99	7	1
100–149	2	0
150–200	1	1
Total.................	25	6

Findings. Associated congenital anomalies occur fairly frequently in these cases, such as cryptorchism, imperforate anus, congenital absence or partial absence of abdominal muscles, urethral diverticulum, vesical diverticulum and so forth.

Urinalysis should be the first examination made because the urine is infected in almost all of these patients. Of this group of 31 cases, pyuria of some degree was present in 30.

Renal function is impaired much more frequently and to a greater degree than in the patients with myelodysplasia. For instance, the values for blood urea in this group (table 7), show 12 to be 50 mg. or more per 100 cc of blood.

The incidence of dilatation of the upper portion of the urinary tract in this series is high, as shown by the results of excretory urography (table 8).

Unfortunately, retrograde cystograms were made in only a few cases in this group, but reflux of medium up both ureters was noted in a high percentage of cases in which the determination was made.

The amount of residual urine is, of course, the most important determination (table 9).

Although the amount may not be large, residual urine was present in nearly all cases and in more than half of this group it varied from 100 to 1,000 cc. It is true that it may be somewhat difficult at times to make an accurate determination of residual urine in young children. Nevertheless, it should be done both preoperatively and postoperatively, for often this is the only means one has to evaluate the success of the operative procedure. If residual urine persists after operation, a second operation should be done.

Cystoscopic findings. It will surprise most readers of this article to know that there were no congenital valves of the urethra encountered in any of these patients. This statement seems even more significant when one recalls that in the clinic cases reported by Thompson in the years previous to this study, there were only 10 cases of congenital valves in 63 cases studied. It was further noted in his series that in the 10 cases in which valves were found there were often other types of obstruction also present that seemed as important as, or more important than, the valves. Why this discrepancy exists between our findings and those reported in the literature is not entirely clear. The most likely explanation is that congenital valves cause death so early in life that most of these small patients must be cared for within the first few days after birth and are not able to be taken on trips to medical centers. The greatest experience with this type of condition therefore would be had by physicians working in large cities and centers of population. We have also wondered if some of the so-called congenital valves diagnosed cystoscopically are nothing more than folds of mucous membrane highly magnified by the small lens cystoscopes. We have on several occasions

TABLE 8 *Condition of kidneys and ureters as determined by excretory urography, group II (congenital obstruction of the vesical neck)*

	MALE	FEMALE
Pyelocaliectasis	21	5
Normal	3	1
Not examined	1	0
Total . . .	25	6

TABLE 9. *Preoperative residual urine, group II (congenital obstruction of the vesical neck)*

	MALE	FEMALE
Patient admitted with suprapubic cystostomy	4	0
Patient admitted with indwelling urethral catheter	1	0
Residual urine not determined .	3	0
Less than 60 cc residual urine . . .	1	1
60–99 cc residual urine . .	1	3
100–599 cc residual urine . . .	13	2
600-1,000 cc residual urine .. .	2	0
Total	25	6

noted such findings with the lens cystoscopes but when examined with the infant direct Braasch cystoscope they were not apparent.

At any rate, the types of obstruction found in our group of cases consisted of such conditions as definite lobar hypertrophies, bars, contractures of the vesical neck, hyperplasia of the "internal sphincter," "redundant tissue at the vesical neck" and normal-appearing vesical necks. *The latter finding should be emphasized*, for occasionally one cannot honestly state that an obstructive lesion can be recognized, visually, yet because there is vesical retention of urine, resection of the vesical neck is indicated and usually eliminates the retention. It is the same situation of imbalance of the detrusor and vesical neck that we have repeatedly emphasized in caring for obscure types of urinary retention in adults. If the vesical neck is weakened by transurethral resection, the bladder is usually able to evacuate its contents.

Some of the more unusual types of obstruction encountered in this group may bear mention. In 2 boys, aged 5 and 8 years respectively, there was what appeared to be a trilobar prostatic enlargement. In the first case 4 gm. of tissue was removed, while in the latter 6 gm. was removed. On microscopic examination of the tissue there was very little prostatic glandular substance present. Most of the tissue was muscle. A brief abstract of one of these cases follows.

Case 3. A boy, 5 years of age, was admitted to the clinic on October 14, 1945. At the time of his admission he appeared acutely ill and had a temperature as high as 104° F. daily. The parents stated that since the age of 6 months the child had had repeated attacks of chills and fever. The most severe attacks had been associated with a temporary inability to void that finally responded to forced fluids and sitz baths. The urinary stream had not been normal since the boy was 6 months of age. It was small and weak, with occasional blood, but there had been no nocturia or bed wetting. He occasionally lost a little urine when awake.

Examination revealed a concentration of urea of 18 mg. per 100 cc of blood. An excretory urogram showed bilateral pyelocaliectasis, grade 2+, with moderate reduction of function of both kidneys. A determination of the residual urine showed 200 cc to be present. There was pyuria, grade 2, and culture of the urine showed Pseudomonas. Blood studies revealed the concentration of hemoglobin to be 10.9 gm. per 100 cc of blood (72.7 per cent); erythrocytes numbered 4,470,000 and leukocytes 14,400 per cubic millimeter of blood. The sedimentation rate (Westergren method) was 120 mm. per hour. There was nothing found on physical or roentgenographic examination to suggest spina bifida or myelodysplasia.

The patient was treated by means of an indwelling urethral catheter, penicillin, sulfathiazole and intravenously administered fluids for a period of eight days. The temperature returned to normal, the patient appeared to be much improved and a urinary output of 1,500 to 2,500 cc per day was maintained.

Transurethral resection was performed on October 22, 1945. The 18 F. cold knife punch was easily introduced through the urethra. There was a very obstructive collar of tissue completely surrounding the vesical neck. It was especially obstructive in the lower half of the circumference just proximal to the verumontanum and looked much the same as a small trilobar prostatic enlargement forming a collar, such as is found in adult men. The entire prostatic urethra was excised, about sixty pieces of tissue, which weighed 4 gm., being removed. On microscopic examination the tissue proved to be hypertrophied muscle.

After operation the fever recurred and for 16 days the temperature fluctuated between normal and 103° F. On the seventeenth postoperative day the temperature returned to normal and the catheter was removed. The results of operation were excellent: the patient was able to void a normal stream and empty the bladder completely. There was no incontinence. The parents were advised to give the patient 3¾ gr. (0.24 gm.) of sulfathiazole 4 times a day on alternate weeks until the urine was clear.

The patient was brought back for re-examination 3 months after dismissal and was found to be in excellent condition. The urine was microscopically and culturally negative The vesical function was normal and there was no residual urine. An excretory urogram showed marked improvement in the kidneys.

Another unusual variety seen in this group is the clinical entity of congenital absence of abdominal muscles. Daut, Kennedy and one of us (J. L. E.) have reported one of these cases previously. The condition is always associated with urinary retention and bilateral hydronephrosis and hydro-ureter. Postmortem examinations have failed to demonstrate the cause of the retention. In such a case encountered in this group cystoscopy showed nothing except a possible "redundancy of tissue at the vesical neck." Transurethral resection eliminated the 400 cc of residual urine. This case is briefly abstracted in the following paragraphs.

Case 4. A male child 3½ years old, of Italian descent, was admitted to the clinic on May 16, 1945. The parents stated that the three chief reasons for seeking medical aid for the child were (1) constant dribbling of urine, (2) recurring episodes of fever, and (3) lack of abdominal muscles.

Information elicited from the parents disclosed that the child had been born at full term by breech delivery. Weight at birth was 8 pounds, 7 ounces (3.8 kg.). At the time of the delivery it had been noted by the obstetrician that the child had "an absence of his abdominal muscles." The child walked at 14 months and talked at 18 months. Abdominal binders made of cloth had been used until the child was 1½ years of age. At that time a corset was made, which proved satisfactory. The child had been immunized against smallpox, diphtheria and tetanus, and had been circumcised shortly after birth. The familial history was unimportant. The father, mother and a year and a half old brother were well developed and normal in every way.

Physical examination disclosed an alert, well-developed, well-nourished child, whose height was 40¼ inches (102.2 cm.) and whose weight was 41½ pounds (18.8 kg.). Physical examination of the child disclosed a large, pendulous, flaccid abdomen which seemed to be devoid of abdominal musculature. A mass which possibly was the right kidney could be palpated in the upper right quadrant should take time at the beginning of the operation to identify them and then he must be careful not to excise them during the resection. If they are excised ureteral reflux will often result and give rise to troublesome infection of the kidneys. To the uninitiated it may sound rather ridiculous to warn against cutting the ureteral orifices, but this is easily done. In most cases much of the resection consists of excising the portion of the detrusor muscle which forms the vesical neck, and often the hypertrophied interureteric bar must also be resected. In many cases the ureteral orifices are so close to the vesical neck as to be injured easily. For this reason the orifices should be accurately identified at the beginning and end of the resection. For the same reason it is wise to make preliminary retrograde cystograms to determine if ureteral reflux exists. If reflux is present one should use more care to avoid excessive distention of the bladder during operation in order to avoid precipitating an acute attack of pyelonephritis.

Postoperative care. Postoperative care is essentially the same as employed in adults after transurethral resection. It is important to obtain good hemostasis at the termination of the operation, as relatively small urethral catheters must be used, which may easily be occluded by blood clots. When a "perineal transurethral resection" has been done the surgeon has the choice of inserting an 18 or 20 F. bag catheter through the perineal incision or a smaller plain or coudé tip soft-rubber catheter through the urethra. If the latter is done, the perineal incision will heal somewhat more quickly but this is of no great importance. If the former method is employed, the catheter is removed from the perineal incision after 24 or 48 hours and a small catheter is inserted through the urethra and left in place until the perineal incision is healed.

The postoperative care is not ended when the surgical convalescence is over and the patient is voiding satisfactorily. Because of the pyelocaliectasis and pyelonephritis present in most of these cases a long period of treatment with suitable urinary antiseptics is indicated. The condition of the urine of these patients should be carefully followed by means of microscopic examination of specimens stained with Gram's stain and by culture. The medication should be changed as necessary to cope with the offending organism.

The treatment of the urinary infections with sulfathiazole or sulfadiazine is usually successful with the exception of Streptococcus faecalis infections, which yield rapidly to mandelic acid therapy provided renal function makes a pH 5.5 in the urine possible. When there is impaired function, penicillin administered by mouth or intramuscularly can be successfully used to get rid of Streptococcus faecalis but will not control the gram-negative organisms. In mixed infections massive doses of streptomycin, 500,000 units intramuscularly four times daily, can be used when other modes of treatment fail. The urine should be strongly alkaline with streptomycin treatment. It is important to remember that crystal-clear urine may contain thousands of bacteria per cubic centimeter. Therefore unless the patient has a sterile urine on culture after discontinuation of treatment for at least two days he should not be dismissed as cured.

The operative results are listed in table 10.

It will be observed that the results are much superior to those in the group of patients with myelodysplasia. Twenty of the 31 patients in this group secured excellent results, while 5 more were markedly improved. Although 1 patient was relieved of his urinary retention, the renal damage was so severe that uremia progressed and the patient died. Examination of the 6 patients in whom only fair or poor results were obtained suggests that reoperation should have been tried in some cases and would probably have met with success.

SUMMARY AND CONCLUSIONS

Urinary stasis in infants and children, in which the causative lesion is below the level of the ureteropelvic junction, may often be relieved by transurethral resection of the vesical neck.

Young people who require transurethral resection may be divided into two groups: (1) those who have vesical dysfunction which results from myelodysplasia and spina bifida, and (2) those who have congenital obstruction of the vesical neck.

Table 10. *Results of transurethral resection, group II (congenital obstruction of the vesical neck)*

	MALE	FEMALE
Good: voids freely, no residual urine, no incontinence	17	3
Improved: residual urine eliminated, but still does not void freely	0	1
Improved: voided well, less than 60 cc residual urine but died in uremia 2 mo. later	1	0
Improved: voids freely, no residual urine, but some degree of incontinence persists	3	0
Fair	1	0
Poor	3	2
Total	25	6

There are two problems to overcome in the group of patients with myelodysplasia and spina bifida: (1) relief of obstruction of the vesical neck and elimination of residual urine (which is essentially the same problem as in cases in which cord bladder results from acquired lesions of the spinal cord) and (2) correction of an incompetent external urethral sphincter. Owing to our inability to combat the latter problem, normal vesical function can be re-established in only about one in three patients of this group.

The group of patients with congenital obstruction of the vesical neck respond to treatment with transurethral resection in a much more satisfactory manner. In more than 2 of 3 patients normal vesical function can be restored. The ultimate course of these patients depends on the amount of renal damage present. Early diagnosis is therefore important. In our group of cases we did not encounter any congenital urethral valves. The type of obstruction encountered consisted of lobar hypertrophies, bars, contractures of the vesical neck, hyperplasia of the "internal sphincter" and redundant tissue at the vesical neck, and "normal-appearing vesical necks."

Complete urologic survey was made in 14 cases, but was interrupted in the others by their transfer to another center. Studies performed included cystoscopic examinations, bladder capacity and residual urine determinations, voiding cystourethrograms, and upper urinary tract studies. Among this group 9 had laminectomies and the lesion was complete in 12 either clinically or by actual inspection. There was 1 lumbar lesion and 2 cervical, 3 upper thoracic and 8 lower thoracic lesions. One of the low thoracic injuries was a partial one.

The usual cystoscopic picture was very characteristic despite the level of the lesion. The mucosa of the bladder showed some degree of cystitis, usually of the catarrhal type. A few had alkaline encrusted cystitis and a large amount of exudate. Increased trabeculation was present in only 3 of 16 cases cystoscoped. In each of these the primary lesion was at a varying level—high or low thoracic, and lumbar. As a rule fine trabeculation was found. In the majority of cases the interureteric ridge was poorly developed and the ureteral orifices were situated in a high or elevated position. The vesical neck was dilated and seemed to be continuous with the posterior urethra. The capacity of the posterior urethra was increased. With the slow installation of fluid it assumed a funnel-shaped appearance, and a distinct groove or depression undermining the posterior lip of the vesical orifice was seen. The supra-montane distance was decreased. In 2 cases there was contracture of the vesical neck.

The residual urine and bladder capacity varied in 14 cases. Most efficient emptying was found with 2 high thoracic lesions and 1 case with a partial lumbar lesion with residual urines of 15 cc. In the lower thoracic lesions capacities ranged from 80 to 400 cc and the residual from 40 to 200 cc. One case with a low thoracic lesion was excluded from the analysis because of his very recent injury. The bladder capacity was 800 cc and the residual 650 cc. He was in the stage of spinal shock and overflow. In 2 cases of cervical lesions the findings were not remarkable.

Voiding cystourethrograms were performed in 14 cases. Incompetence of the internal sphincter with dilatation of the vesical neck was found in 12 cases. Spasm or contracture was found in 2. The external sphincter was spastic (fig. 1, *A*) in 10 cases, negative in 1, dilated in 2 and not visualized in 1. The dilatation was noted in 2 cases with high thoracic lesions (fig. 1, *B*). Fuzziness of the margin of the bladder indicating cystitis was present in 7 cases. Ureteral reflux was found in none.

Flat films of the urinary tract in 35 cases revealed the presence of renal calculi in 4 and bladder calculi in 7 cases, an incidence of 11.4 and 20 per cent respectively. Retrograde pyelograms were performed in 13 cases, intravenous pyelograms in 4. Normal pyeloureterograms were obtained in 8 cases. Hydronephrosis was present in 7 cases; bilateral in 4. Dilatation of the ureters occurred bilaterally in 8 cases. Usually hydronephrosis when present was associated with dilatation of the ureter. In only 2 instances did it occur alone. Dilatation of the ureter unassociated with hydronephrosis occurred in 7 individual ureters. No definite correlation could be made with the level of the cord lesion, nor was there evidence of intrinsic obstruction.

In 23 individual ureters catheterized, white blood cells above 10 per high power field were found in 11 instances Negative cultures were found in 8 instances. The most common organisms cultured were B. coli and Pseudomonas aeruginosa, and each occurred in 8 instances. Both occurred simultaneously in 2 cases. Staphylococcus albus was cultured in 4 cases and occurred in association with Pseudomonas aeruginosa. Proteus vulgaris was present in 1 culture. Function tests, as judged by the appearance time of indigo carmine, were normal, in most cases. Evidence of severe renal impairment was present in only 1 case. The reaction of the urine was usually acid. This contrasted sharply with studies on the bladder urine, in which case alkalinity was more common.

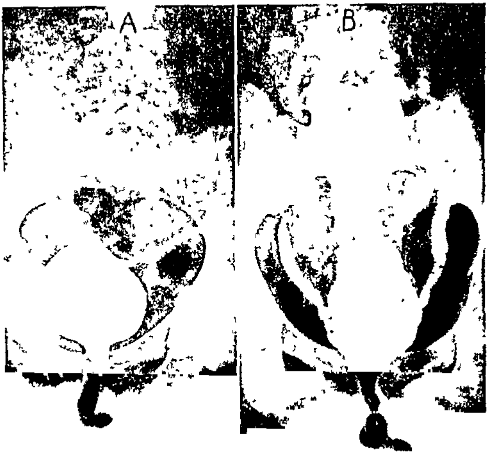

FIG. 1. *A*, Voiding cystourethrogram in a patient with a lesion of D11, illustrating spasm of external sphincter. *B*, Voiding cystourethrogram in a patient with a lesion of D7, demonstrating relaxation of external sphincter. Filling of ureters is not caused by ureteral reflux but pyelographic study.

Penoscrotal fistulas were present in 2 cases on admission, and were due to the rupture of a periurethral abscess. Epididymitis occurred in 4 cases and in 1, went on to abscess formation. These could be traced to previous prolonged urethral catheter drainage.

BLADDER PHYSIOLOGY

In general the function of the bladder is the retention and evacuation of urine. The nerve supply to the bladder is through the sympathetics and parasympathetics. The parasympathetics, or pelvic nerves, arising from the second, third and fourth sacral segments are the *more important*. They are the motor nerves of the bladder and also carry the sensation of distention. Their stimulation causes contraction of the detrusor muscle and relaxation of the so-called internal sphincter. The vesical neck or internal sphincter seems to be only the margin of the detrusor muscle or continuation of the detrusor fibers. The sympathetics are deemed to play a relatively unimportant role. Their function is to carry pain and temperature sensation and they also innervate the trigone, ejaculatory duct and blood vessels. The action of the trigone is considered unimportant unless obstruction in the form of a median bar is present.

The external sphincter is composed of striated musculature and, as striated musculature in general, does not have the ability of constant maintenance of tone. It is innervated by the pudendal nerve, arising from the second and third sacral segments in that portion which has to do with somatic functions. Ordinarily, the external sphincter opens automatically and reflexly as the detrusor contracts. It can be closed but not opened spontaneously. Even when the vesical neck is distorted, however, the external sphincter can control continence.

According to Rose, micturition is a voluntary-involuntary reflex. First, the voluntary lowering of the perineum initiates the secondary involuntary bladder contraction. At the proper time the voluntary perineal muscles (pubo-coccygeus, pubo-rectalis, ilio-coccygeus and muscles within the urogenital diaphragm) relax. Contraction of the trigonal muscle depresses and spreads the internal opening, and involuntary contraction occurs. The nerve supply to the involuntary mechanism lies in the sympathetic and parasympathetic systems. He believes the innervation is crossed since both types of fibers are found in each nerve trunk.

DISTURBED BLADDER PHYSIOLOGY

With injury to the cord the stage of retention occurs. Sir John Thomson Walker found in 30 consecutive cases that this may last from 1 to 55 days. In a larger series, he found the shortest time to be 1 day, the longest 18 months until reflex micturition occurred. In spinal shock the external sphincter is thrown out of function. The detrusor does not contract. With progressive distention of the bladder and rise in pressure a small amount of urine may be forced past the resisting sphincter. Three stages are ordinarily described—complete retention, retention with overflow and finally reflex micturition. Riches found that in lesions above L1, 5 cases developed this reflex micturition in an average of 12 weeks; 9 cases with cauda equina lesions averaged 26 weeks.

Injuries above L1 lead to the eventual production of the so-called automatic bladder. In supralumbar lesions, the reflex is intact, although there is no inhibition from the higher centers. The bladder is stimulated to contract by the stretch reflex at pressures ranging from 11 to 15 mm. of mercury. As a rule, the higher the lesion the better is the automatic action, with the possible exception of lesions above C7. Lesions from C7 to D7 result in the most effective form of automaticity. There is as a rule little residual and the contractions are more efficient. From D7 to D12 there is usually a larger residual and less efficient contraction.

In supralumbar spinal cord injuries, the inhibitory influences from the higher centers are lost, although the involuntary portion of the reflex as described by

Rose is present. With high thoracic lesions, the automatic bladder function is apparently better than in low lesions, residual urine and bladder capacity determinations more nearly approach the normal. This may be due to the eventual re-establishment of old pathways and intersegmental synapses; the greater the distance above the lumbar area in the thoracic cord, the more effective the bladder function. In 2 cases with high thoracic lesions voiding cystourethrograms showed dilatation of the external sphincteric area, rather than spasm as is seen in the low thoracic lesions. The ability of spasm of the external sphincter to cause retention and control continence, even in a badly distorted vesical neck, is well known; and spasm of the external sphincter is of frequent occurrence in these patients. It is possible that in low thoracic lesions in which there is no hope of recovery, that the answer to the problem of retention difficulties may be in the attack on the external sphincter mechanism, possibly by section of one or both pudendal nerves. The incontinence and dribbling that might occur could be controlled by the use of a Cunningham clamp. Interruption of the presacral nerve has not been of any dramatic benefit in these cases. The above findings and hypothesis would have to be substantiated not only by a much larger series, but by further experimental work.

With lesions below the D12, the sensory and motor pathways are interrupted leading to the autonomous bladder. When the lesion is below the conus, inhibitory impulses from the higher centers are still present. Otherwise contractions depend on the local nerve plexuses within the bladder wall. As a rule the contractions are poor although to some extent under voluntary control; the stream may be fairly good by straining. Emmett states that there is increased tone, decreased capacity, large residual urine and hypertrophy of the vesical neck. In complete cauda equina lesions, Watkins explains the resistance to flow as being due to the elasticity of the tissues in the region of the triangular ligament.

TREATMENT

The correct method of treatment of the recently paralysed bladder is a subject that is open to much debate. Almost complete unanimity of opinion exists on the subject of intermittent catheterization. However, this method is mentioned only to be condemned because of the inevitable development of infection. Manual expression has had its advocates although this method is used but rarely. The disadvantage in this form of therapy lies in the fact that it takes prolonged periods of time for reflex micturition to occur. Until then, the bladder empties by overflow and by pressure over the lower abdomen. With pressure there is the danger of ureteral reflux taking place. Eventually, the urine becomes grossly infected because of the large residual present.

Another method is continuous urethral catheter drainage. The limit of tolerance to the use of the urethral catheter is approximately 6 weeks. The disadvantage of this method is the probable development of such complications as urethritis, periurethritis, epididymitis, orchitis and penoscrotal fistulas. Infection is difficult to control when a urethral catheter is present. Its use is definitely contraindicated when stricture, urethritis or periurethritis is present. In such cases, Lewis recommends the use of perineal urethrostomy drainage. He states that there is no leakage, no further dressings are required, the catheter is easily replaced and when drainage is discontinued normal voiding occurs. If a urethral catheter is used the smallest caliber Foley type is recommended. The use of adhesive to fix the catheter in place is unsatisfactory because of the accumulation of secretion and the frequency of erections in these individuals. Changes of the catheter should be made at least once weekly and be performed aseptically. The anterior urethra should be irrigated with a suitable antiseptic at each change. The combined use of the urethral catheter and tidal drainage is another method of keeping the bladder clean. However, urethritis and other complications can still occur. The bladder mucosa must not be overstretched since ulceration of the bladder mucosa can easily occur. It is a difficult matter to keep a tidal drainage apparatus functioning properly and it requires constant and trained supervision. This method may be of value, however, in the prevention of the contracted bladder.

The most acceptable form of therapy is suprapubic cystostomy. This should be done as early as possible in the presence of definite cord injury and is also recommended when infection occurs after other methods have been used. Suprapubic drainage will not prevent subsequent reflex micturition. The advantages, in fact, are obvious—the complications that occur with the use of a urethral catheter are obviated. The bladder can easily be kept clean and infection avoided. Changes of catheter are made with facility. A low placed stoma should be avoided and the opening should be made midway between the symphysis and umbilicus. This will help prevent the formation of a contracted bladder and there will be less leakage around the tube.

The return of bladder tone can be determined readily by filling the bladder slowly and noting whether or not spontaneous voiding occurs. If a suprapubic tube is used, it is drawn tightly against the stoma. With a urethral catheter voiding occurs about the catheter, or the catheter may be withdrawn and the bladder stimulated to empty by pressure. Cystometric determinations are usually unnecessary. The question then arises as to how the bladder opening should be closed. Various methods were tried and the most effective and simplest was found to be the surgical closure of the wound. This was rapidly accomplished, usually no anesthetic was required, and there was no subsequent leakage about the wound. Other procedures employed included that of allowing the wound to drain suprapubically until the stoma closed. This required copious dressings, was uncomfortable to the patient, and the stoma took prolonged periods of time to close. Still others were closed by urethral catheter drainage with or without packing of the suprapubic sinus. Many of these closed only to reopen. In a few cases with a small fistulous opening, fulguration of the mucosal surface of the fistula was performed cystoscopically.

Nesbit and Gordon and others have called attention to transurethral resection of the bladder neck in spinal injury cases. Many will find it difficult to envisage why a widely dilated neck which is present in most of these cases should be subjected to this procedure. However, even minimal obstruction may place a great burden on an already overburdened bladder. There is little objection against this operation in clearly defined instances as contracture or persistent spasm of the vesical neck, median bar formation or prostatic hypertrophy—or where there is evidence of increased trabeculation or unusually large residual urines. Bumpus et al. found their best results were obtained in lesions of the cauda equina. Higher lesions do not yield as spectacular results although there is definite evidence of diminution of residual urine These patients were enabled to void at 4 hour intervals and were often enabled to go through the night without soiling the bed. If this procedure is to be performed, the resection should be as complete as possible and should be performed before secondary atony occurs.

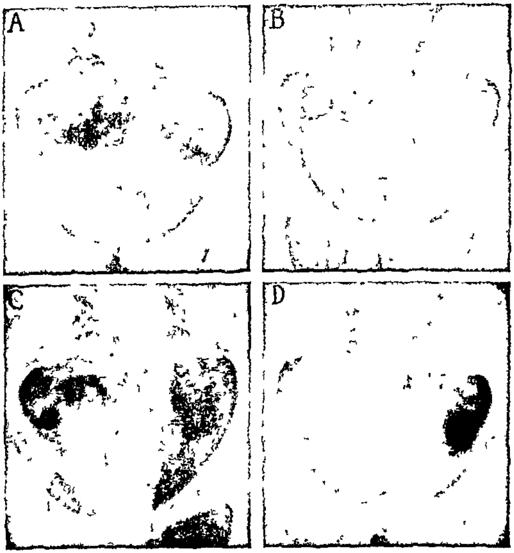

FIG. 2. An example of dissolution of bladder calculi with Suby's solution G. *A*, Prior to onset of irrigations *B*, After 12 days of irrigations *C*, After 37 days of irrigations. *D*, No evidence of calculi in films taken on forty fourth day.

The daily care of the paraplegic should be mentioned. A general training program is prepared for each patient. The ill effects of prolonged immobilization are well known. Patients are encouraged to use the wheel chair, sent to the gymnasium for muscular development and taught, if able, to walk with the aid of crutches and braces. Massage of the lower extremities and passive exercises are performed daily. When in bed the patients are turned frequently in efforts to prevent decubital ulcers. Various urinary appliances were used when the patients were out of bed. These included Cunningham clamps, male rubber urinal appliances, and ordinary male urinals. We have found the Cunningham clamps satisfactory in most instances. Care should be observed in their use. They should be just tight enough to occlude the urethra, be removed every hour or two and not allowed to remain in place all night.

The frequency of formation of bladder and renal calculi in these cases is well known. Prophylactic measures are taken to prevent their occurrence. The diet is a neutral ash, high caloric, and high protein one. Fluids are forced to 4000 cc daily. The more dilute the urine, the less chance is there of calculi occurring. Infection is an important factor in the formation of calculi and therefore frequent observations are made on the status of the urine. For the routine treatment of infections of the urinary tract the drugs used were sulfadiazine, mandelamine and pyridium. Sulfadiazine was found to be the most effective for the ordinary infections. Streptomycin has been found to be effective in the treatment of Aerobacter aerogenes and Proteus ammoniae infections by Pool and Cook. In certain resistant bladder infections good results have been obtained with irrigation and instillation of tyrothricin solutions. When catheters are in place, the bladder is irrigated twice daily with boric acid solutions by trained attendants. At times, with a severe bladder infection present, a closed drainage system is set up and the patient is taught to irrigate the bladder every 2 to 3 hours. Frequent flat films of the urinary tract are made to rule out the presence of calculi and if indicated cystoscopic study is performed without hesitation.

When renal calculi are formed the treatment is usually surgical. Conservative measures, however, should first be tried. We have observed a large 3 cm. stone pass spontaneously into the bladder in 1 case. Seven of our cases had bladder calculi. Disintegration of these calculi with Suby's solution G was effective in all and was reported elsewhere (fig. 2). The procedure is a simple one. The solution is allowed to run into the bladder through a 2-way Foley catheter at the rate of 80 drops per minute. Solution of the calculi occurred from 6 to 44 days, averaging 14 days, dependent on the size and number of the calculi. Where alkaline encrustations are present this solution is very satisfactory.

Penoscrotal fistulas usually require surgical closure. Diversion of the urinary stream may be necessary in these cases. The presence of epididymitis and orchitis require the usual measures.

SUMMARY

The urologic problems encountered in a group of 35 spinal injury cases are presented. Normal and disturbed physiology of the bladder is discussed. Studies were made on both the upper and lower urinary tract. The treatment of these cases is outlined. The possible role of the external sphincter mechanism in determining the degree of efficiency of the automatic bladder is discussed.

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THE TRANSVESICAL REPAIR OF VESICO VAGINAL FISTULA

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The surgical repair of vesicovaginal fistulas has challenged the ability of the surgeon ever since van Roonhyse in 1672 suggested a planned surgical procedure for their closure.[1] He approached the fistula by the vaginal route. This approach was used exclusively until 1888 when Trendelenburg[2] successfully repaired a fistula by the transvesical route. Since that time transvesical repair of these fistulas has been more popular in Europe than in this country. This is possibly due to the example set by Marion Sims in this country which began with a successful vaginal repair in 1849. This was 41 years before Trendelenburg presented in detail the advantages of the transvesical approach. When he presented his work, he gave great credit to the men who had perfected the vaginal repair, and apologetically suspected that they would consider the transvesical approach a rash undertaking.

The American literature over the last 20 years shows the popularity of the transvesical approach and the number of cases so operated on to be slowly increasing. Sears,[3] in 1929, collected 48 cases, mostly European, in which there were 40 cures, 7 failures and 3 deaths, and added 2 cases of his own. To these can be added 8 cases by Lower[4] in 1935, 2 cases by Quinby[5] in 1936, 4 cases by Douglas[6] in 1937; 17 cases by Farsht[7] in 1940, and 3 cases by Sharp and Green[8] in 1946, and others. Although this is not an impressive number of cases, it is worth noting that they were cured at 1 operation. To these we would like to add 8 cases of vesicovaginal fistula successfully repaired at 1 operation by the transvesical approach.

Because of the leakage of urine into the vagina, this predominantly urological lesion is considered a gynecological problem by the patient and her physician. Therefore, urological surgeons seldom have the opportunity of primarily repairing these fistulas. They usually see them for cystoscopic consultation, or after they have been repeatedly operated on or complicated by other urological problems.

Vesicovaginal fistulas occur in the practices of the obstetrician and gynecologist. It is natural that these men who have been trained to do vaginal surgery should pursue the repair of this lesion by the vaginal approach. They maintain, and correctly so, that it is the most direct and safest approach to the lesion, and because of this fact they justify a repetition of the operation until successful. This idea was more nearly correct when these fistulas resulted from

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[1] Cited by Kelly, H. A.: Trans. Am. Gynec. Soc., 37: 8, 1912.
[2] Trendelenburg, F.: Medical Classics 4 (part 2): 964–988, 1940.
[3] Sears, N. P.: Am. J. Obst. & Gynec., 18: 267–273, 1929.
[4] Lower, W. E.: Am. J. Surg., 28: 234–241, 1935.
[5] Quinby, W. C.: New Eng. J. Med., 214: 415–417, 1936.
[6] Douglas, M.: Surg. Gynec. & Obst., 65: 534–535, 1937.
[7] Farsht, J. J.: J. Urol., 44: 279-300, 1940.
[8] Sharp, R. F. and Green, M. M.: Urol. & Cutan. Rev., 50: 632–636, 1946.

ill-managed labors, and occurred low on the bladder floor. Today two-thirds of all vesicovaginal fistulas are produced by pelvic or vaginal surgery. These fistulas occur higher on the bladder wall and higher in the vaginal vault. The repair of surgical fistulas is not only more difficult due to their position, but the vaginal approach is further embarrassed by the distortion resulting from the partial amputation of the vaginal vault and the absence of and the fixation of the cervix. In order to meet this situation, the gynecologist has resorted to extensive vaginal incisions to properly visualize the fistula.

The merits of the vaginal approach need no defense. Counseller[9] says that 85 per cent of most small vesicovaginal fistulas can be closed at 1 surgical procedure, especially if previous repeated attempts at closure have not been made. He reported that of 181 cases, 98 had from 1 to 10 attempts at closure elsewhere, whereas 61 had 2 to 6 attempts at closure at the Mayo Clinic. This is good evidence that each failure to close a fistula makes each succeeding repair more difficult and increases the likelihood of failure.

In a large number of collected cases by Miller[10] extending from 1854 to 1934 in which the vaginal approach was used chiefly, the cures averaged 82.2 per cent. He was unable to note the number of attempts that failed before closure was completed. We are well aware that most of these fistulas can be cured by the vaginal approach, but our meager experience does not allow us to subscribe to the idea that the vaginal approach is so much safer or preferable to the transvesical that it should be repeated until the surgeon, patient and tissues are exhausted.

The successful surgical repair of vesicovaginal fistula is greatly aided by 1) an accurate diagnosis and 2) adequate preoperative preparation.

The diagnosis of simple vesicovaginal fistula is easily made by the use of colored fluid or air injected into the bladder and noting the point at which it escapes into the vagina. This procedure establishes only the fact that there is a fistula. It does not tell all that should be known with reference to the origin of the fistula in the urinary tract. The fluid may enter the vagina by the way of the uterus, cervix, urethra or bladder, or directly from the ureter. It is important that a cystoscopic examination be performed to locate accurately the site of the fistulous opening in the bladder and its relation to the vesical sphincter, the ureters and trigone. The possibility of multiple fistulas should be kept in mind and a search made to determine their exact location and course. The condition of the bladder as a whole should be observed for contracture, atrophy, tumor, stone and infection. The fistulous opening should be examined for slough, incrustation, and carcinoma if suspected. The patency of the ureters and the condition of the kidneys should not be neglected. When the fistulous opening is found to lie along the course of the ureter, in the trigone or above it, the ureters should be retrocatheterized to determine whether it is involved in scar of the fistula or whether it has fistulized into the bladder fistula. When there is a ureterovesicovaginal fistula present, intravenous pyelography may be inadequate to determine the involvement of the ureter. Incomplete knowledge of the origin of the fistula or of multiple fistulas may lead to ill-planned surgical procedures. A correct diagnosis of the location and the pathological changes associated with a fistula may be a determining factor in selecting an approach for surgical repair.

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[9] Counseller, V. S.: Surg. Gynec. & Obst., 74: 738–745, 1942.
[10] Miller, N. F.: Am. J. Obst. & Gynec., 30: 675–695, 1935.

The preoperative preparation includes the removal of bladder and vaginal disease that might interfere with a successful repair of the fistula. This usually means the eradication of the infection of the bladder and vagina. It is important that the closure of the fistula be made in a sterile field and with healthy tissues. An infected bladder mucosa or urine is a most common finding and is a cause of some recurrences following repair. Today we are fortunate that they both can be sterilized quickly and satisfactorily by the use of the sulfa drugs, acidifying agents and the antibiotics. These drugs have undoubtedly increased the percentage of primary successful repair of vesicovaginal fistulas. These drugs are most valuable in the reparation of those neglected cases which have been denied operation because of infection. One of our cases had a badly infected bladder and a large sloughing fistula for 4 years. There were incrusted ulcers and edema of the vulva and thighs. The vagina was distorted from transverse bands of scar which almost bisected the vagina. She was treated for 1 year before closure was attempted.

All of our patients with vesicovaginal fistula were white, and their ages varying from 28 to 51 years. In 5 cases the fistula followed hysterectomy; 1 occurred postpartum, 1 resulted from cautery of the cervix with the high frequency current, and 1 occurred spontaneously. The time that elapsed between the development of the lesion and admission to the urological service was from 6 to 18 months in 4 cases, 4 years in 2, 8 years in 1, and 9 years in another case. The fistulas varied from $\frac{3}{8}$ inch to $1\frac{1}{4}$ inches in diameter. All of the fistulas resulting from hysterectomy were located high on the edge of the trigone or above it on the bladder wall and communicated with a distorted and fixed vaginal vault. In 2 cases the fistula emptied into a pocket in the vaginal vault, and the pocket in turn opened into the vaginal cavity at a lower level. One obstetrical fistula was located in the midtrigone.

A short summary of previous operative attempts to close these fistulas will give a better idea of the material with which we had to work. Five patients had had a total of 15 attempts to close a fistula by the vaginal route; 1 patient, in addition to 4 vaginal operations, had had a transabdominal repair of the fistula; 1 had had 2 vaginal repairs followed by a transperitoneal and a transvesical closure, and 11 minor attempts such as cautery and minor surgical procedures, which were unsuccessful. One patient with an obstetrical fistula had had a supravaginal hysterectomy and a repair of the fistula at the same time which failed. In all, 19 surgical attempts to close 6 fistulas had been performed. There were 2 patients in this series in which no attempt to repair the fistula had been made at the time we saw them.

Very little has been added to the fundamental concepts of the surgical closure of vesicovaginal fistulas during the last century, but many technical modifications to improve the application of the basic principles have been presented. We wonder if some of them have not been developed to the point that the basic principles of closure have been slighted.

Our first experience in the repair of vesicovaginal fistula had a definite urological aspect, and occurred in a patient who had had 4 vaginal attempts to close a fistula located above the trigone and over the course of the right ureter. Following the last operation pain developed in the right flank, accompanied by chills and fever. Examination revealed a strictured ureter and a functionless right kidney. The bladder was opened widely. The fistula was embedded in dense scar and the ureter could not be catheterized. The ureter was then exposed extraperitoneally. The terminal 2½ inches of it were embedded in scar, above which it was dilated and thick. The ureter was tied and cut, and the lower end dissected down to the bladder. The bladder and vaginal wall were mobilized. The vaginal roof was closed and the section of the bladder containing the fistula removed, and the bladder wound closed with interrupted catgut sutures. The mucous membrane was closed tightly with a continuous chromic suture. The pyelonephritic kidney was removed later. Recovery was complete. In this case, we unwittingly used the fundamental technical principles necessary for the repair of vesicovaginal fistulas, namely 1) denudation of fistula; 2) mobilization of vaginal roof and bladder muscle; 3) closure of both without tension. A technique that will accomplish these concepts should be successful in a high percentage of cases. We have approached this problem from the standpoint of primarily repairing the bladder muscle. Therefore, any technique that would bring together viable bladder muscle without tension, at the time of repair or following the closure, should be fundamentally sound. We believed that our experience would enable us to carry out the fundamentals of repair, technically better, through a transvesical approach.

After a surgical preparation of the vagina, it is packed with gauze or an inflatable bag is introduced if the fistula is low. A longitudinal suprapubic abdominal incision is made to expose the bladder which is opened widely. The location of the fistula is determined. If it is near a ureter, it is identified by a ureteral catheter. A sharply curved forceps is introduced through the fistula, if possible, and opened. Denudation of the edge of the fistula is performed between the opened blades of the forceps. Traction to elevate the fistula is never made on any structure except the vaginal roof. Mobilization of the bladder muscle is partially, not completely, carried out at this time. The vaginal roof is now closed with interrupted chromic catgut sutures which are not introduced through the vaginal roof. After the vaginal roof is closed, mobilization of the bladder is continued until the edges of it can be coapted without tension. Mobilization of the bladder is carried out with as little trauma to it as possible. Mobilization of the bladder wall should never be too extensive. If it is, a dead space will be left for the accumulation of blood, and it may interfere with the blood supply to the bladder wall. The bladder is then closed with chromic sutures (which are never tied tightly), using just enough to coapt the tissues. The mucosa is closed with a continuous suture of fine catgut catching a few fibers of bladder muscle to keep it from dipping into the wound. The anterior bladder wound is then closed about a de Pezzer catheter fixed in the dome of the bladder. The abdominal wound is closed routinely. The patient is then returned to a bed with a split mattress and placed in the prone position. This position is maintained from 4 to 10 days after which she is allowed to turn on her side. In 2 cases, one with Proteus infection of the bladder, and the other with a gram positive coccal infection of both kidneys, we maintained a constant drip irrigation of boric acid solution introduced through a urethral catheter and out the cystotomy tube. Cystotomy drainage has been maintained from 8 to 17 days. The vagina was irrigated daily.

The only exception to the procedure described above was the use of silk in 3 cases to close the bladder muscle. The only complication that occurred was in a case of Proteus infection. The sutures did not remain buried and concretions formed about them. We removed the sutures with a resectoscope armed with a broken loop. One prong of the loop was slipped under the suture, the loop elevated, and the cutting current turned on. The sutures were quickly cut and came away with the loop. Quinby[5] has shown that the closure of the vaginal roof is not essential for the successful repair of a vesicovaginal fistula. We were unable to close the vaginal roof in 2 of our cases.

We made no attempt to close the tissue planes at different angles. This has been stressed by some surgeons. We closed the vaginal roof and bladder muscle in the plane that insured freedom from tension.

Fear has been expressed in some quarters that the transvesical approach would leave the patient with 2 fistulas. The suprapubic fistulas in all these patients closed promptly. None of these patients leaked urine during convalescence and no fistula has broken down since operation; none has developed a stone in the bladder. All of these patients were completely cured at 1 operation.

COMMENT

The surgical repair of vesicovaginal fistula has been and will continue to be beset with disappointments, regardless of the skill of the operator, the approach or technique of closure employed. The vaginal approach will continue to be the one of choice. We believe that our meager experience will justify the transvesical approach to vesicovaginal fistula 1) where the vaginal approach has repeatedly failed, 2) in high, fixed fistulas, 3) where the vaginal exposure is inadequate. We contend that the transvesical approach with cure is preferable to repeated failures by the vaginal route, even if ultimately successful. Two patients in this group were wet over a period of 17 years. Both were cured by transvesical closure in 3 weeks. (These patients did not criticize the transvesical approach.) The urological surgeon using a transvesical approach must plan his attack so that failure is reduced to a minimum. Repeated transvesical closures are more hazardous to the patient than repeated vaginal closures. It is more worthy of the urologist to accept only those cases that have resisted vaginal repair, if he is going to use the transvesical approach, than to fail where the vaginal approach is indicated.

The treatment of vesicovaginal fistula is a urological problem. The problem is to repair a hole in the bladder. The transvesical approach affords adequate exposure and good visualization of the structure to be repaired. It is the natural approach for the urologist. We wish to agree with Kirwin and Lowsley that this lesion offers to the urologist a challenge which he should not hesitate to accept regardless of the approach which is necessary for a successful closure. We believe that the transvesical approach is justifiable in selected cases. We believe this small contribution will substantiate this premise.

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AIR BUBBLES IN PROSTATIC RESECTION

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To many resectionists the air bubbles in the operative field are an annoyance and a severe handicap. The condition is likely to be particularly troublesome when low pressure of the distending fluid is used.

It is, of course, well known that water with high pressure flowing through simultaneously the inlet of the bakelite sheath and the tubes in the electrotome will force the bubbles from the operative field into the bladder. However, if the water is used through two high pressure lines at the same time, over-distention of the bladder is almost certain to occur.

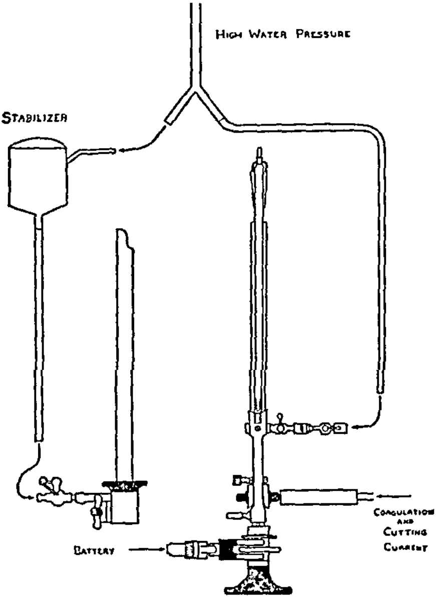

Fig. 1

From observation of many operators, I am convinced that over-distention of the bladder is the cause of much morbidity and even mortality. At the present time, I believe it is Enemy No. 1 in prostatic resection. On the contrary I have found that by the use of low pressure postoperative anuria, shock, and hemolytic jaundice can be prevented.

Furthermore, high pressure is unnecessary as bubbles can be dispelled, bleeding points visualized, and a clear vision of the field obtained while using mucosa. Small hooks or rake retractors are then used to elevate the vesical neck for close inspection.

When bleeding appears well controlled, a 24 F. Foley catheter with a 30 cc bag is inserted through the urethra and into the bladder. The tip is cutoff for additional drainage. A heavy silk suture is passed through the tip of the catheter and out the suprapubic incision This suture can be used for guiding in a straight catheter later, if desired, or for manipulating the bag if bleeding is troublesome. The bag is injected with 10 cc of water and drawn into the fossa. Several small strips of oxidized cellulose (Oxycel) are packed into the fossa and additional water injected into the bag to lightly distend the fossa. A stab wound in the upper portion of the bladder is made with a hemostat and a No. 20 or No. 22 straight two-eyed catheter drawn into the bladder for suprapubic drainage. The silk suture is also drawn out through this opening. The original bladder incision is closed in 2 layers with plain 0 catgut. The drainage tube is brought out the midline and the fascia closed with interrupted sutures of chromic 0 catgut. Muscles or subcutaneous tissues are not sutured. The skin is closed with clips.

POSTOPERATIVE CARE

The patient receives a portion of a liter of 5 per cent glucose in normal saline intravenously during the operative procedure. This is continued when he returns to his bed. An additional 2 liters of 5 per cent glucose in distilled water, each containing 25 cc of 95 per cent ethyl alcohol are administered on the operative day. Small amounts of water and coffee are given by mouth, and if active peristalsis is present, soft diet is allowed on the operative night. Carbogen is used each hour for pulmonary hyperventilation. The patient is encouraged to actively move about in bed as soon as the effects of the spinal anesthetic have worn off. The bladder is irrigated sparingly with normal saline, and only to keep drainage free from clots. Morphine and atropine are used for pain, but the intravenous use of alcohol makes the use of narcotics minimal.

Ambulation is begun on the first day, and the patient is encouraged to take a few steps. The water is usually released from the bag, and the catheter strapped in place with adhesive tape. If bleeding is not troublesome, the suprapubic tube is removed on the second or third day. In 80 per cent of the cases there was no suprapubic leakage of urine. The patient is helped to the lavatory for stool on the third day. We believe that straining on a bedpan is more detrimental than being up for stool. The psychic value of getting up to the lavatory is very great.

By the fourth day, the patient is semi-ambulatory with his catheter draining into a small bottle which is suspended from the waist. When the suprapubic wound is dry for 3 days the catheter is clamped for 1 hour periods. If the wound remains dry the catheter is clamped for 2 hour periods on the following day and then removed. If the patient voids easily and without great urethral dribbling he is discharged home. He reports to the office in a week or 10 days, and is followed for 3 months. Urinary residual, infection and urinary control are checked as well as the blood picture and general condition. The patient is not discharged until a full sized sound is passed into the bladder.

DISCUSSIONS OF TECHNIQUE

Transverse incisions have many advantages. They are anatomically and physiologically sound. Exposure is markedly facilitated since all traction is lateral. The vertical tension of the rectus muscles and the normal transverse line of skin tension makes closure easier and makes early ambulation feasible. A high transverse incision in the bladder avoids the prevesical space. All of our skin wounds have healed by primary intention except at the site of the drain.

The most troublesome bleeding comes from the vesical neck in its inferior portion. The blood supply to the hypertrophied prostate has been well demonstrated by Flocks. Preliminary incision with an electrosurgical knife gives a smooth vesical neck, helps seal off small vessels and avoids tearing into the trigone which may bleed profusely. Bleeding from the fossa is controlled by contraction of the capsule, by the Foley bag and by Oxycel.

The closure of the original bladder incision is important. The leading of any sort of a drainage tube through an incised, manually traumatized bladder wound is likely to favor formation of a temporary sinus tract. A stab wound made with a hemostat tends to separate interlacing muscle bundles which rapidly contract and close as soon as the tube is removed.

The use of intravenous alcohol postoperatively is very helpful. Alcohol has sedative and analgesic properties as well as caloric value. The respiratory rate and tidal exchange remain the same or are increased. It increases the dilatation of the blood vessels and possibly the coronary arteries. The patient has a mild euphoria.

There are several commercial forms of alcohol for parenteral administration, but we have merely mixed 25 cc of 95 per cent ethyl alcohol in a liter of fluid. This is given in about 1½ hours.

The value of early ambulation is well established and applies particularly to elderly patients.

RESULTS

This technique has been used on a consecutive series of 34 suprapubic prostatectomies. We have had no deaths. Two patients have been discharged on the seventh postoperative day, and 1 patient remained 19 days as the longest stay, due to small suprapubic leakage. The all over average is slightly less than 10 days.

There were 3 complications of note. One postoperative epididymitis caused considerable fever and discomfort, but resolved without drainage and the patient went home on the thirteenth postoperative day. There was 1 postoperative psychosis which required full restraints for 5 days, but the patient cleared spontaneously and has apparently been normal since. Abdominal distention was very persistent for 4 days in one patient. Average hemoglobin loss was slightly more than 10 per cent. In patients with low hemoglobins, preoperatively, this was replaced by transfusion. Individuals with relatively high hemoglobins before surgery showed return to normal within 4 or 5 weeks with the use of iron by mouth.

SUMMARY

An improved technique of suprapubic prostatectomy is described. This procedure is not radically new, but entails transverse incisions, control of hemorrhage under direct vision, the use of hemostatic agents locally, closure of the original bladder incision, and suprapubic drainage through a stab wound and very early ambulation. Morbidity and complications have been much less than with other techniques that we have used.

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COMPLETE OCCLUSION OF THE VESICAL ORIFICE FOLLOWING SUPRAPUBIC PROSTATECTOMY: REVIEW OF THE LITERATURE AND REPORT OF THREE CASES

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Complete occlusion of the vesical orifice is a very rare complication following suprapubic prostatectomy. A thorough perusal of the literature on obstruction to urination following suprapubic prostatectomy confirms this belief. Some of the authors writing on the latter subject, nevertheless, treat it as a not uncommon complication of suprapubic prostatectomy. Various grades of obstruction to urination do follow suprapubic prostatectomy and lesser grades of obstruction are rather frequent, but complete occlusion of the vesical orifice has rarely been reported. Cabot, nevertheless, has stated: "Complete closure of the neck of the bladder after prostatectomy . . . has occurred many times in my experience." Post-prostatectomy obstruction is a complication that was considered important and not unusual by Thomson-Walker. His technique of open suprapubic prostatectomy, first performed in 1916, was strongly advocated as the technique of choice in order to prevent post-prostatectomy obstructions as well as to more efficiently control hemorrhage. Nevertheless, careful scrutiny of the literature revealed postoperative vesical neck obstructions to be a carefully guarded secret of prostatic surgery.

Very few references to postoperative complete occlusions have made their appearance in the medical literature. In the American and English literature, the most extensive collection of cases was that made by Thomson-Walker. He studied 75 cases of postoperative vesical neck obstructions, 7 of which were complete occlusions. Gordon (1916) has the earliest reference to 2 cases of complete occlusion following suprapubic prostatectomy in the American literature. Mills published the earliest references in the English literature, when in 1914, he reported 2 cases as occurring in his experience. Young published 1 case in his *Practice of Urology* in 1926. Power reported 4 cases of complete occlusion in 1939. Thompson, in 1934, cites 1 case in the *Proceedings of the Staff Meetings, Mayo Clinic.* Irwin, in 1926, also reported 1 case of complete occlusion. Dakin reported 2 cases in 1930. Millin, in 1942, also had 2 cases to report of complete occlusion out of 53 cases of obstruction. He claimed a 2 per cent incidence of post-prostatectomy obstruction in the best hands. Coutts, in 1934, also had 1 case to report. Thus, a total of 26 cases have been reported in the American and English literature, including the 3 cases herein reported by the authors.

Three cases of complete occlusion following suprapubic prostatectomy are being presented in order to point out one of the more infrequent complications encountered in this frequently performed operation by the trained urologist as well as the general surgeon.

CASE REPORTS

Case 1. S. G. (8401) was first seen in 1944 at the age of 62. At that time, he had a history of increased frequency of urination of a progressive nature of 3 years duration. Recently, he had been complaining of nocturia 1–3 times, diuria 5 times, with scanty voidings, some hesitancy; and after voiding, he had the sensation that he did not completely empty his bladder. The stream was poor with terminal dribbling. There was no hematuria.

The physical examination was essentially normal except for the rectal examination which revealed the prostate definitely enlarged to a second degree and the enlargement was uniform. The prostate was soft, doughy and elastic in consistency with no areas of hardness suggestive of malignancy. A residual urine of 90 cc was found. The diagnosis was that of benign prostatic hypertrophy, seond degree.

On November 10, 1944, a 1-stage suprapubic prostatectomy and bilateral vasectomy was performed and a moderately enlarged prostate with an anterior lobe which caused a very tight vesical orifice was removed. No urethra beyond the prostatic portion was removed in the procedure. The lobes were soft and doughy. Microscopically, it proved to be an adenocarcinoma of the prostate.

On the third postoperative day, the packs were removed and 10 days later the suprapubic catheter was removed. Following this, he was unable to void per urethram. Under sodium pentothal anesthesia, an attempt was made to dilate the urethra with sounds and filiforms, but this failed. When the patient attempted to void, no urine came through the urethra, but a stream did issue from the suprapubic sinus.

The bladder was then opened on December 5, 1944, and with the index finger exploring the bladder, no evidence of a vesical orifice could be found. An incision was then made through the obstruction over the tip of a sound introduced through the urethra. The vesical orifice was then dilated to 28 F. and a catheter inserted. The suprapubic wound healed and on December 24, 1944, the penile catheter was removed and voiding began, but without control.

Subsequent dilatations of the urethra resulted in partial incontinence, but by March 1945, he had regained his control. Dilatations after this were performed with a 20 F. sound for a slight obstruction which persisted. At his last examination, there was no nocturia or frequency. Rectally, there was no induration present in the region of the prostate, and his condition on December 20, 1945 (one year after operation) was excellent.

Case 2. W. B. (8534), aged 70, had a 10 year history of frequency of increasing severity. Nocturia 2–4 times was present with some hesitancy and terminal dribbling. There was no hematuria. There was some urgency and, on one occasion, there was acute retention, but this was not complete.

The physical examination was essentially normal except for the rectal examination which demonstrated the prostate definitely enlarged. There were no areas of hardness suggestive of malignancy. Cystoscopy was performed and 120 cc residual urine was found. There was a large middle lobe with slight bulging of both lateral lobes in the posterior position. There was no evidence of stone or tumor mass. A few trabeculations and cellules were seen. The diagnosis was benign prostatic hypertrophy, second degree.

A 2-stage suprapubic prostatectomy and bilateral vasectomy were performed on February 27, 1945, and March 6, 1945. The prostate was found to be soft and doughy and 1.5 cm. of urethra distal to the prostate was removed in the enucleation of the prostate. The suprapubic sinus drained freely for 10 days, when acute retention developed necessitating the insertion of a Kelly clamp into the suprapubic wound, dilating it and permitting the escape of a large amount of retained urine. No urine passed per urethram. All subsequent attempts to pass urethral instruments failed.

The bladder was again opened on March 23, 1945. A sound was passed through the penis only to meet an obstruction at the vesical orifice. At operation, it was found that a complete occlusion formed at the vesical neck. A complete layer of tissue was present, completely obliterating the expected site of the urethral opening into the bladder. This area was incised over a previously inserted penile sound and a catheter was then inserted. The suprapubic wound healed well and the penile catheter was then removed. Voiding soon started with a good stream, but some dribbling was present.

On his discharge from the hospital, he was voiding well but with only fair control; incontinence increased after he became ambulatory and this necessitated his wearing a urinal. After repeated dilatations up to 26 F., better urinary control developed and the dribbling diminished considerably. After his last dilatation with a 26 F. sound, he dribbled very little and was able to void in a good stream. He was also able to start and stop the stream completely during the act of micturition and voided as much as 350 cc at a time. The last examination was made in December 1946.

Case 3. S. S. (8889), aged 64, was admitted to the Sinai Hospital on January 10, 1946, with a history of frequency and dribbling following urination, of 4 years' duration. He also had nocturia 4 times, hesitancy and a weak stream. For these complaints, he had been given by his physician 2 to 3 mg. of stilbesterol daily for 1 year. This improved his stream but resulted in the development of bilateral gynecomastia. Stilbesterol was then discontinued and the stream became weaker.

Physical examination revealed an enlarged saddle hernia in the right groin, a hydrocele of the right cord and bilateral varicose veins of the legs. Rectal examination also revealed a spastic external sphincter, internal and external hemorrhoids, and a prostate that was uniformly enlarged, soft, doughy and elastic in consistency. The median furrow was obliterated. There were no hard nodules present suggestive of malignancy. Cystoscopic examination revealed slight bulging of the right and left lateral lobes of the prostate and a definite median lobe posteriorly. No evidence was found of a stone or tumor mass in the bladder. Many trabeculations and some cellules were present. No diverticula were seen. There was only slight bulging of the prostate into the urethra. The diagnosis was benign prostatic hypertrophy, second degree.

A 2-stage suprapubic prostatectomy, a hydrocelectomy and a partial bilateral vasectomy were performed on January 11, 1946, and on January 18, 1946. The prostate was found to be rather fibrous and bulged into the vesical orifice and into the prostatic urethra. The prostate was removed in 2 sections, the right lobe being larger than the left.

On the fourth postoperative day following the second stage, prostatic packs were removed and the patient bled excessively; but this was soon controlled. Eight days later, he was permitted to sit up at the side of the bed but started to complain of tenderness, redness, swelling and pain in his left leg. The impression was that phlebothrombosis had developed and early thrombophlebitis. On the thirteenth and fourteenth postoperative days, the patient voided on several occasions up to about 125 cc of urine. Thereafter, he was unable to void and continued to drain profusely suprapubically. Attempts at dilatation were unsuccessful even under sodium pentothal anesthesia. A cystourethrogram was taken on February 4, 1946, with the aid of a catheter placed into the bladder through the suprapubic fistula. This film revealed complete separation of the bladder from the vesical orifice (fig. 1).

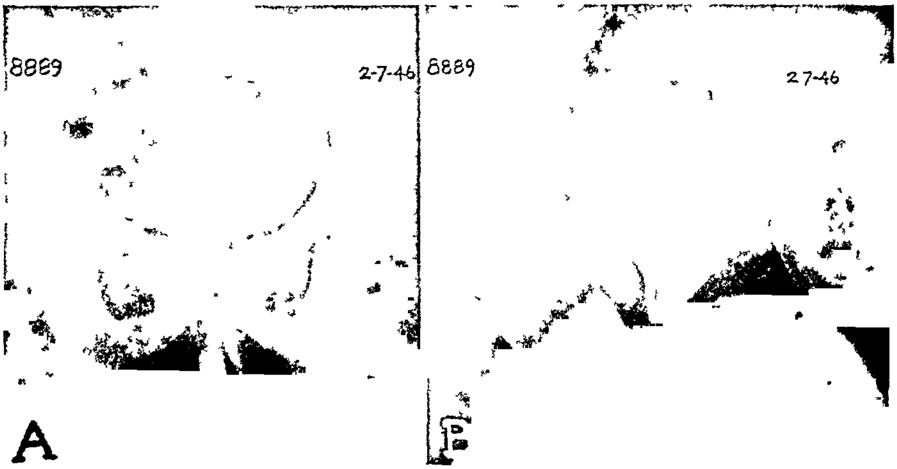

FIG. 1 Case 3, No 8889. *A*, Combined urethrogram and cystogram through suprapubic catheter. Antero-posterior view. Separation of opaque solution by occluding vesical diaphragm at upper part of prostatic fossa is clearly visualized. Solution in urethra is arrested at external urethral sphincter. *B*, Oblique view of combined cystogram and urethrogram. Showing clearly separation of bladder from urethra by diaphragm at prostato-vesical junction.

A suprapubic cystotomy, performed February 8, 1946, revealed complete occlusion of the vesical orifice. The obstruction consisted of complete overgrowth of the bladder mucosa as a diaphragm over the vesical orifice. The site of the vesical orifice was revealed by a slight depression 5 mm. deep. The obstruction was then broken through over a sound placed into the urethra. The vesical orifice was then dilated up to 28 F. and a 18 Foley catheter was inserted into the bladder through the urethra.

Five days later, he began to complain of pain in his legs and thighs and a diagnosis of osteitis pubis was made. On the eighth postoperative day, the catheter was removed and he voided for 2 days, at the end of which time the suprapubic wound opened and drained profusely. A Foley catheter was again inserted, but on its removal only small quantities of urine were voided. Suprapubically, he still drained profusely. Cystoscopic investigation was then performed and a vesical calculus was found and removed. Thereafter, he improved steadily, voided well, without incontinence but frequently, and in a good stream. He received a course of deep roentgen-ray therapy which caused the osteitis pubis to heal.

DISCUSSION

Various degrees of obstruction from large caliber strictures to small caliber strictures are extremely frequent following suprapubic prostatectomy. In fact, in the postoperative management of a patient who has undergone prostatectomy, the passage of sounds to establish the adequate patency of the vesical orifice should be routine and performed at least once before final discharge from the surgeon's care.

A great deal of the early work on obstructions following suprapubic prostatectomy was done in France and England. The first extensive and exhaustive investigation of this subject in England was undertaken by Thomson-Walker of St. Peters Hospital, London. In 1921, he reported on 16 cases of obstruction. In 1927, he reported on 60 cases. In his Littsomian lectures in 1930, he reported 75 cases of severe obstruction following suprapubic prostatectomies which he saw as consultant. He found in these cases either fibrous contraction at the site of operation or new growth in the wall of the prostatic bed, either in the form of a recurrent benign hyperplasia or a malignant growth. He found the site of obstruction rarely at the distal end of the prostatic cavity. Only 4.3 per cent of the 75 cases under his observation had the obstruction at the membranous urethra. "The point of narrowing in 85.5 per cent of the cases is at the opening of the bladder into the prostatic cavity." In 7 cases (9.3 per cent of his series) the internal meatus was completely obliterated, so that no trace of it could be discovered. In one of these cases, a false passage had been tunnelled through the bladder base and opened into the bladder behind the trigone; in another, a false urethra tunnelled through the right lateral wall of the bladder.

PATHOLOGY

Complete occlusion following suprapubic prostatectomy occurs almost exclusively at the junction of the bladder with the prostatic cavity. All the reported cases, including the three reported by the authors, have had the occlusion at this site (fig. 2). Theoretically however, a complete obstruction or obliteration of the urinary channel can occur postoperatively when the prostatic bed is the involved site. In these latter cases, dense scar formation, an extreme degree of the more frequently encountered obstruction, may result in occlusion of the passages. The removal of a cylinder of urethral mucosa distal to the prostate thus denuding the urethra; and the presence of infection, residual urine and gauze in the prostatic cavity all will stimulate the proliferation of fibroblastic the prostatic fossa can be cut away by scissors or knife. Thompson handled this remaining portion of occluding diaphragm by resection per urethram. The catheter is left in place from 10 to 14 days and voiding usually starts as in a primary suprapubic prostatectomy.

PROGNOSIS

The prognosis in these cases of complete occlusion is good. Thomson-Walker treated, by open operation, 40 cases of severe post-suprapubic prostatectomy obstructions including 7 of the complete occlusion variety, and all were cured. His procedure was suprapubic cystotomy and incising the diaphragm over a sound passed into the penis and the utilization of a catheter.

PROPHYLACTIC MEASURES

Post-suprapubic prostatectomy obstruction has been often encountered and feared and many procedures have been adopted in an attempt to prevent its occurrence. So, too, these procedures attempt to prevent the occurrence of complete occlusions. Thomson-Walker, in 1916, devised an open operation for a suprapubic prostatectomy. In this procedure, tags and strips of mucosa, muscle or prostatic tissue, etc., are exposed and if present, are carefully clipped away and the mucous membrane trimmed at the edge of the cavity. A wedge (a "V" open anteriorly) is taken out of the posterior canopy and frequently two sutures are taken just posterior to 3 and 9 o'clock for the control of hemorrhage. Other techniques to eliminate these mucosal flaps have been suggested. The French, as reported by Dax, have followed the technique advocated by Albarran and divided the posterior shelf with a bistoury. They also advocated splitting the bladder mucosa behind the adenoma either by scissors or guided knife and they they enucleated the prostate in 1 piece—doughnut fashion—starting posteriorly and working forward and *thus removed the prostate with "all of its* mucosal roof" intact.

More recently, Harris in 1927, introduced his technique of suturing the mucosal diaphragm of the internal vesical orifice directly to the free edge of the membranous urethra just severed, and bringing the mucosal flaps at each side together with a figure of eight suture over an indwelling urethral catheter.

None of these procedures, though, have been completely successful in obviating complete occlusion. Millin reported a case following the procedure of Harris. Power advocates the Harris procedure, if possible, but makes it mandatory that all suprapubic prostatectomy procedures be completed by leaving an indwelling catheter in situ.

Certainly, if a large flap can be felt to remain following suprapubic prostatectomy, or if it is noticed that a large portion of the membranous urethra has been removed with the prostate, one should anticipate complications in the form of an obstruction, partial or complete. The immediate placing of an indwelling catheter into the bladder per urethram, will preclude the formation of an obstruction.

SUMMARY

Complete occlusion of the vesical orifice following suprapubic prostatectomy is a very rare complication.

Three cases of complete occlusion of the vesical orifice following suprapubic prostatectomy and their successful treatment are reported.

In all the American and English literature only 26 cases, including those reported herewith by the authors, have been recorded.

All cases of complete occlusion reported have had the occluding diaphragm of mucosa at the vesicoprostatic juncture.

Complete occlusion is the result of the approximated flaps of bladder mucosa becoming united in the presence of strong contraction.

When a persistent suprapubic sinus is present, investigate for obstruction below.

Persistent instrumentation in the face of complete occlusion at the vesical orifice may result in serious complications.

Treatment consists in suprapubic cystotomy and incising the diaphragmatic obstruction over a urethral sound.

Prognosis in all cases is excellent.

Prevention of complete occlusion following operation is possible by the utilization of an indwelling urethral catheter. This is suspected when a large overhanging diaphragm is present. The prostatic fossa and diaphragm contract in purse-string-like fashion and obliterate the prostatic cavity from which the prostate was enucleated.

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EPITHELIOMA OF SCROTUM[1]

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The purpose of this paper is to record observations made on 27 patients with epithelioma of the scrotum. When this first occupational cancer was described by Potts in 1832 it is reasonable to suppose that there was but one causative factor known because he named it "Chimney Sweeps Cancer." While chimney soot continued to cause the greatest number of scrotal cancers in England for about 75 years, early in the twentieth century growths resulting from the rubbing of rough trouser seams on the scrotum (Mule Spinners Cancer) and prolonged exposure to tar and paraffin became respectively first and second in frequency. It would seem that in New York in the years between 1926 and 1947 inclusive additional etiological factors were present because 10 different cancerigenic substances were associated with the development of tumors in 22 patients, while in 5 patients the causative agent could not be recognized.

Generally speaking contact with petroleum and its products, especially in the refineries, appears to be the most common cause of scrotal cancer at present in the New York neighborhood. Workers in these industries describe how their work clothes become saturated with oil so that oil is in contact with their skin during the entire work period. At the end of the day they change their clothes without washing the oil from their bodies, and they hang up their work clothes preparatory to wearing them the next day. (Case 1 is typical of many.)

In addition to the mineral oils other well known cancerigenic agents such as tar, pitch, crude wool and soot affected these patients. At variance with recorded observations is the fact that 8 patients with scrotal cancers had been employed where there were no demonstrable occupational hazards. The disease therefore is not acquired exclusively through occupational contacts. Three of these men had tumors caused by medical therapy; twice Fowler's solution taken for psoriasis played a prominent part (tar ointment also was used by one), while the third had repeated roentgen irradiation of the scrotum followed by telangiectases, fibrosis and a neoplasm. In another individual, who was a merchant, long standing dermatitis due to a severe fungous infection of the scrotum and thighs was accepted as the cause of his tumor.

It is likely that in some otherwise unexplained instances chronic irritation of the scrotum resulting from general uncleanliness may have caused cancers. Probably this factor also has contributed to the serious outcome in many cases in which recognized cancerigens played the more important part.

CASE REPORTS

Case 1. S. K., a 62 year old Lithuanian, had been a "paraffin press runner" for 25 years. During this time he worked in a room in which paraffin was pressed into various forms. With his clothing saturated, all of his skin was in contact with melted paraffin throughout the day. From time to time "oil boils" appeared on his hands. Finally a small "wart" appeared on the left side of his scrotum. It was found to be a squamous cancer.

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[1] Read at annual meeting, North Central Section, American Urological Association Cleveland, O., October 23–25, 1947.

Case 2. A. K., 34 years of age, Polish, had worked in a factory for 12 years making conduit pipes out of pitch. He stated that his work clothes were soaked with pitch daily. After working 10½ years under these conditions some small hard lumps appeared on the scrotum. When they ulcerated they were treated with x-rays which appeared to do no good. They were excised and squamous carcinoma found. Sixteen months after the scrotal lesions appeared the patient noticed lumps in his groins. Pathological diagnosis was squamous carcinoma, grade 2.

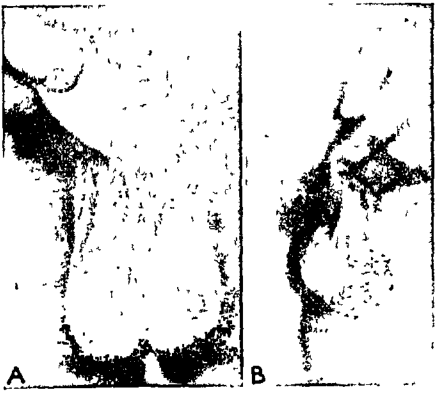

FIG. 1. *A*, Appearance of usual scrotal cancer, which first appears as a wart, and enlarges as an ulcerating warty overgrowth. *B*, Scrotal cancer, which appeared as an area of keratosis.

Case 3. J. F. I., aged 48, a white American cashier, had suffered from psoriasis since the age of 12. For 26 years he took Fowler's solution, discontinuing it in 1930. In 1933 a carcinoma was removed from the abdominal wall. Since then many lesions have appeared on the skin in various parts of his body. On admission he had tumors on the chest wall, both groins, back, heel and scrotum. There were many keratoses on the dorsi and palms of his hands. For approximately 10 years he had treated the psoriasis and arsenical keratoses with tar ointment. He died in 1940 when a metastasis in the right groin from the scrotal tumor eroded the femoral vein.

Case 4. L. C. S., aged 55, a white American packer in a florist shop for 37 years, at the age of 35 began to suffer from psoriasis. Beginning at the age of 10 he took Fowler's solution. The dose varied from 4 drops 3 times a day to 12 drops 3 times a day until puffiness of his eyelids appeared. He is still taking it.

Four years after beginning with Fowler's solution "rough spots" appeared on his palms and soles. A year later the first finger of each hand was amputated because of epithelioma and at the same time 2 epitheliomas were excised from the left palm. At the age of 52, twelve years after taking arsenic, the terminal phalanx of the right fourth finger was removed for carcinoma. Two years later a similar sore appeared on the dorsum of the third finger of his left hand. It has been treated with topical applications. At the age of 65, twenty-five years after beginning the use of Fowler's solution, a squamous carcinoma, grade 2, was removed from the scrotum. He died of carcinoma of the pleura without any residual scrotal disease.

Case 5. B. E., aged 60, a white American motorman, in 1919 was given roentgen radiation for eczema of the scrotum. The lesion improved. It recurred, however, in 2 years and was again irradiated with almost complete disappearance for 10 years. At the end of this time, about 12 years after the first treatment, telangiectatic areas appeared on the skin of the scrotum. These intermittently broke down and healed. Beginning in 1937, about 19 years after irradiation, the ulceration became larger, bleeding occurred and the areas have become painful. Microscopic diagnosis was squamous carcinoma, grade 2.

Case 6. P. F., aged 55, a white American merchant, never worked with any cancerigenic agents. He was a stout man and suffered from a fungous infection of each groin for about 20 years. In July 1945 he first noticed a small pimple on the scrotum. He applied a red salve until January 1946, although there was no benefit. The sore gradually became larger. In February 1946, seven months after the initial lesion was discovered, enlarged nodes appeared in the left subinguinal region. The patient was treated by local excision of the primary tumor and bilateral radical groin dissections. Nine months after removal of the primary tumor there was a recurrence in the scrotum. It was removed. Now a year later, the patient shows no evidence of local recurrences or metastases.

As shown in table 1, the patients, with few exceptions, were between 50 and 70 years of age, and had been in contact with cancerigenic agents for about 25 years. Two patients, however, were but 32 and 34 respectively when their tumors appeared and they had been exposed only 10½ and 12 years to pitch and machine oil.

The well known sensitivity of the skin in persons with fair complexions probably is an etiological factor in scrotal cancer but little evidence along these lines can be established by studying a small group. The majority of the oil workers were Poles, while the remainder of the patients were Americans or Irish. No Latin nations were represented and there were no Negroes.

Another feature clearly shown by this group and not previously emphasized was the high incidence of multiple primary tumors since of the 27 patients 8 had proved primary cancers in addition to those of the scrotum. Three oil refiners had skin tumors of the arms, eyelid and lower lip respectively. In the 2 patients in whom arsenic was the causative factor the scrotal tumors were but one of many skin cancers. Two men had tongue cancers while one had cancer of the pleura. In some of these cases, such as the oil refiners and the arsenic users, the different tumors had a common etiology Whether or not the same holds true for the other patients is interesting to speculate on but not to be demonstrated until more sensitive chemical tests are developed

Symptoms After many years contact with the cancerigenic agent the majority of the patients first noticed itching of the skin of the most dependent portion of the scrotum (case 7) At the same time or usually within 6 months a small warty growth was found where the itching was most intense Other patients who saw their tumors early described them as "pimples" or "small sores" or "small lumps" An area of keratosis was described as "a small rough sore" Tumors discovered at a later stage were almost always ulcerated and were described as "small sores"

TABLE 1 —*Etiology of 27 cases of scrotal cancer*

	AGE OF PATIENT	OCCUPATION	CANCERIGENIC AGENT	DURATION OF EXPOSURE WHEN TUMOR APPEARED
1	62	Crude oil distiller	Crude oil	40 years
2	59	Roofer	Tar	36
3	34	Machinist	Machine oil	12
4	55	Merchant	Fungus infection thighs and scrotum	20 plus
5	55	Merchant	Unknown	
6	34	Laborer	Pitch	12
7	53	Petroleum refiner	Petroleum	30
8	56	Petroleum refiner	Oil and coke	25 plus
9	66	Wool sorter	Wool oil?	40
10	60	Tool sharpener	Oil and emery powder	29
11	50	Oiler	Lubricating oils (heavy and light)	31
12	59	Blacksmith	Grease and oil	25 plus
13	64	Machinist (bearings)	Lubricating oil	27
14	62	Paraffin press runner	Paraffin	25
15	57	Oil refiner	Petroleum	25
16	51	Oil refiner	Petroleum	25
17	60	Oiler for engines	Lubricating oils	25
18	59	Porter watchman	Unknown	
19	60	Presser on dresses	Mechanical?	25 plus years
20	65	Hatter	Unknown	25 plus
21	50	Machinist	Petroleum (oil)	20 plus
22	48	Cashier	Arsenic (Fowler's Solution) Tar ointment	26 10 plus
23	55	Florist	Fowler's Solution	25
24	65	China decorator	Unknown	
25	60	Motorman	Roentgen radiation	18
26	52	Laborer cleaning boilers and chimneys	Chimney soot	25 plus
27		Only information is pathological diagnosis of squamous carcinoma grade II		

There is no evidence that the primary tumor alarmed any of the patients In most cases nothing was done until the warty lesion had grown to about 2 cm in diameter and had ulcerated. These developments usually required from 3 to 12 months. Soon after ulceration occurred the tumors became painful and they appeared to grow more rapidly. The patients, almost without exception, now began to apply home remedies, principally salves, without benefit. In a few instances electrocaogulation given by physicians did no good.

After being aware of the primary tumors for a period varying between 4 months and 120 months with 12 months about the average, the patients found painless swellings in the inguinal regions. These were metastases. Smaller inflammatory nodes, easily palpable by the medical examiner, were never noted by patients in this group.

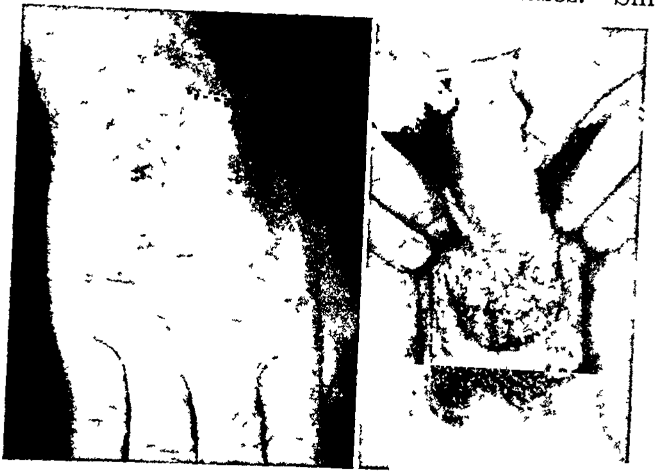

FIG 2. Primary squamous cancers on hand and scrotum of a petroleum distiller

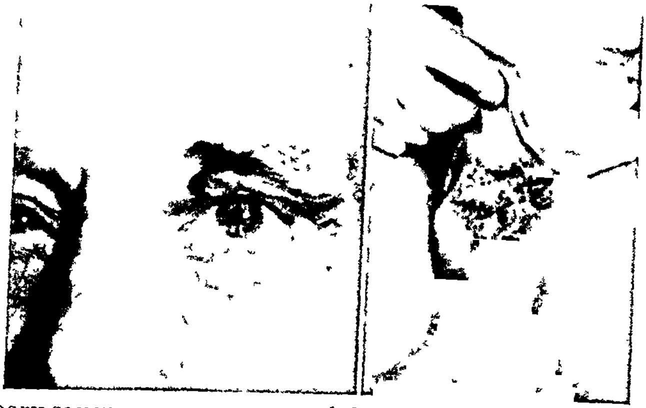

FIG. 3. Primary squamous cancers on eyelid and scrotum of a petroleum distiller

Case 7. A. B., aged 59 years, white roofer, was employed for 36 years constructing tar roofs. At the end of that time he noticed itching and discomfort of the most dependent part of the scrotum. After the itching had continued for 2 years he noticed bleeding and tenderness on the right side of the scrotum. A tumor 2 cm. in diameter was removed and it was found to be an epidermoid carcinoma, grade 3. There was no evidence of metastases. The patient continued to work with tar. Four years and 3 months later another squamous carcinoma

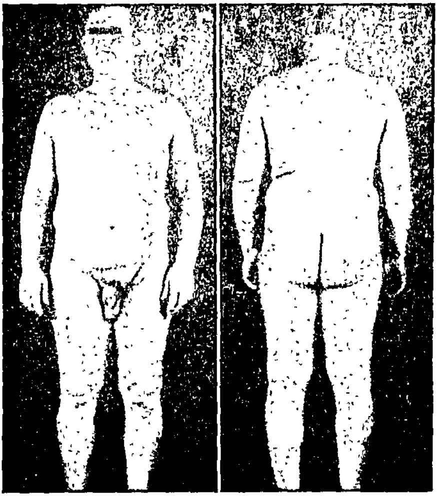

FIG. 4. Multiple areas of keratosis and squamous cancer caused by prolonged treatment with arsenic (Fowler's solution).

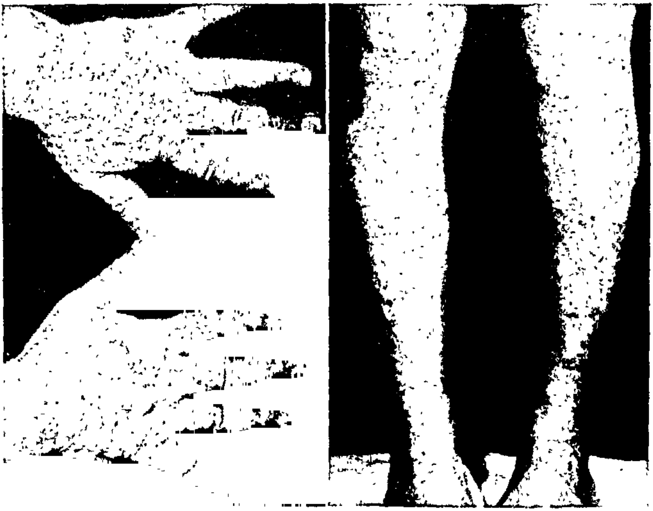

FIG. 5. Hands and legs of patient shown in figure 4

was removed from the left side of the scrotum. He has been well for 2 years and 3 months since his second operation.

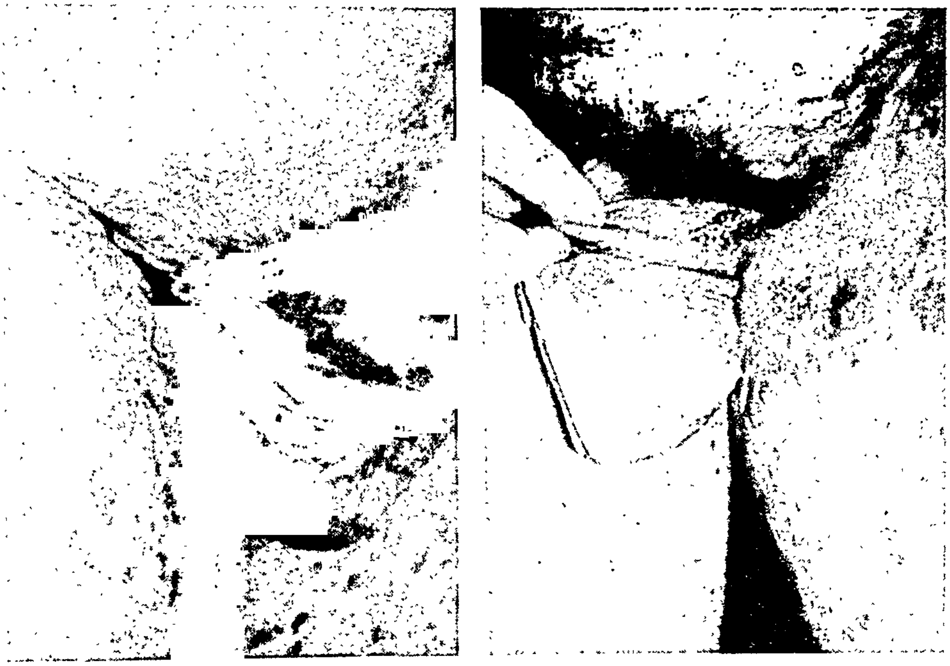

FIG. 6. Cancers on right and left sides of scrotum respectively of patient shown in figure 4.

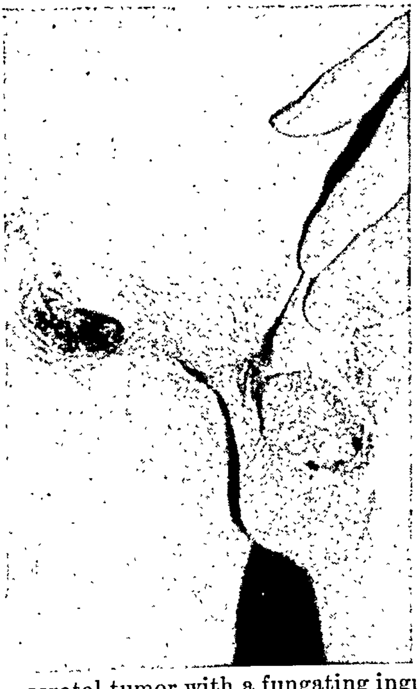

FIG. 7. Primary scrotal tumor with a fungating inguinal metastasis

Cases 8 and 9 illustrate respectively rapid and slow development of scrotal tumors.

Case 8 A W., a 55 year old Jewish salesman, never was employed with carcinogenic agents In October 1945, he noticed a small sore on the scrotum In December, 2 months later, it was excised In February 1946, only 4 months after discovery of the primary tumor, lumps appeared in both groins He was treated with bilateral groin dissections Metastatic squamous carcinoma was found He has been well for 2 years

Case 9 A McB , 60 years old, Irish oiler of stationary engines for 25 years In 1921 (15 years ago) a small ulcerated lesion appeared on the right side of the scrotum Eight years later, in 1929, it was operated upon in a hospital but a similar lesion recurred a year later In 1931, ten years after the small ulcer first appeared, he noticed lumps in his right groin These slowly enlarged over a period of 5 years, when he fell while at work and scraped the skin from his right groin It bled profusely Examination showed advanced bilateral groin metastases, 16 years after a scrotal lesion first appeared

Pathology The great majority of squamous carcinomas in these patients were of grade 2 malignancy Three were of grade 1 and three were of grade 3 No significant differences could be observed in the natural history of the tumors of different grades of malignancy or in their response to treatment because the groups were too small and because the behavior of many grade 2 tumors differed strikingly Extension of metastases beyond the inguinal regions was observed in but 1 patient This tumor was of grade 3 malignancy and was discovered in the lung and left supraclavicular fossa

Case 10 W G , aged 60, a white Russian presser of dresses, in December 1933, had a pea sized tumor removed from the scrotum It was found to be a grade 3 squamous carcinoma One year later it was found necessary to remove the entire right scrotum, both testes and spermatic cords, and radically dissect both inguinal regions Postoperative roentgen radiation was given There has never been a local recurrence but the patient entered the hospital 5 years later with an extensive tumor in the lung and several nodes in the left supraclavicular fossa An autopsy showed that the lung tumor was secondary to the tumor of the scrotum

Diagnosis Although the history of long exposure to a cancerigenic substance followed by a warty tumor of the scrotum should prompt a physician to suspect the presence of either a cancer or a precancerous condition, such is not always the case and our records show the loss of much valuable time while pursuing inadequate therapy before the diagnosis was established If one hesitates to excise the entire growth promptly, one should not wait before removing a specimen for microscopic examination Wasting time studying the differential possibilities or making therapeutic tests loses the few chances for a cure these patients may have had

Treatment The only curative therapy for an epithelioma of the scrotum is wide surgical excision In addition to topical applications of all kinds used without success, electrocoagulation was found inadequate Fifteen patients in this group received roentgen radiation There was no evidence that it caused regression of either the primary tumors or inguinal metastases

When the scrotal tumor is removed a safety zone of normal tissues at least 1 cm. wide should surround the lesion on all sides. Sometimes the gubernaculum testis is infiltrated and one or both testes must be sacrificed.

It is difficult to postulate rules for the treatment of the regional lymphatics. Fungating primary tumors usually give rise to inguinal adenopathy but the enlarged groin nodes are not always cancerous. There is no evidence that removal of noncancerous regional nodes increases the chance of cure and the operation is so often followed by considerable disability due to obstruction of lymph channels that it should not be done unnecessarily. It seems characteristic of metastases from squamous cancers, whether of scrotum, penis or lip, that early spread involves single nodes and causes them to enlarge and harden considerably so that the clinical diagnosis of metastasis is easy to make relatively early. With this aspect of the disease in mind, and especially if the patient can be kept under close observation, it appears safe to recommend that the inguinal metastases should be demonstrated by aspiration biopsy before groin dissections are performed. On the other hand there is considerable evidence that unrecognizable extensions from even a small primary tumor may have occurred when the patient first seeks medical advice. This is a strong argument for routine removal of the lymphatics. Review of our cases of squamous carcinoma of scrotum and penis shows that of the patients first seen with inguinal adenopathy about one half had metastases. These figures suggest that if routine groin dissections were performed about one-half would be useful. However, this study also showed that when dissection of regional nodes was not performed until histological proof of their cancerous involvement had been obtained in no case did metastases subsequently develop beyond the groins. Probably because the writer is able to observe closely the great majority of these patients and because he has unusually experienced pathologists to interpret aspiration biopsies, he awaits histological verification of metastases before operating upon the groins.

As soon as metastases have been discovered, however, radical dissections should be performed. In doing this operation the first incision extends mesially from the anterior superior spine of the ilium to a point 2 cm. above the pubic tubercle. Carefully dissecting from this line, one removes all of the subcutaneous fat, lymphatics, and fascia overlying the muscles and great vessels of the anterior aspect of the upper one-third of the thigh. The inguinal ligament is then cut across above the femoral canal and all lymphatics accompanying the iliac vessels are removed. To facilitate this dissection the abdominal muscles may be divided. Care should be taken to avoid injury to the bladder which is always in or near this operative field. When one groin has been found to be invaded there is great likelihood that the condition is bilateral. Even so it is best in the aged and debilitated to operate upon each side at different times. The operative mortality should be low. No deaths followed groin dissections in this group.

Results. That epithelioma of the scrotum is a serious disease is shown by the fact that of the 27 patients only 8 lived 5 or more years after treatment at the Memorial Hospital.

Table 2 shows the period of survival of the 11 patients first seen without demonstrable metastases and of the 16 who were found to have extensions to the groins at their first hospital visit. Although 2 patients with metastases when first seen died of other diseases 5 and 6 years respectively after groin dissections there are only 6 patients now living without evidence of disease 5 or more years after their first treatment at the Memorial Hospital. Four of these men were seen without metastases and have had none while two have survived bilateral groin dissections for proved cancers for 11 and 13 years respectively. The treatment of 1 patient (case 11) was unusual.

Case 11. H. K., an American, 57 years of age, had been employed in an oil refinery for 25 years. He said that during this time his clothing and especially his trousers were saturated with oil. Finally he noticed a small wart on the lower scrotum. It itched and grew. In 3 months it ulcerated and grew more rapidly. When first seen there were firm nodes in the right groin. Microscopic examination showed infiltrating squamous carcinoma, grade 2. In March 1935, the primary tumor and the left testis to which it was attached were removed. Three months later a bilateral groin dissection was performed. In 2 months there was a proved recurrence in the left side directly over and attached to the femoral vessels. Eleven gold radon seeds were implanted superficially and the tumor disappeared. The patient is now living without evidence of disease 11 years after this highly unorthodox procedure.

TABLE 2.—*Patients now living without evidence of disease*

11 patients first seen with no demonstrable metastases													
Years of life	1	2	3	4	5	6	7	8	9	10			
Number of patients	1	1	1		1	1			1	1			
16 patients first seen with inguinal metastases													
Years of life	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of patients	2	1									1		1

SUMMARY

Observations have been recorded from the study of 27 patients with epithelioma of the scrotum. While the most common causative factor was prolonged exposure to petroleum and its products, other occupational hazards such as tar, pitch, crude wool and soot demonstrated cancerigenic properties. Eight patients acquired scrotal cancers without any industrial cancerigens. Of these 3 were the result of medication, 2 with arsenic (Fowler's solution), the other from roentgen radiation. Eight patients had primary cancers in addition to those of the scrotum.

In most cases after many years' exposure a warty growth appeared on the most dependent portion of the scrotum. In 3 to 12 months it had ulcerated and become painful. These growths were not affected favorably by topical application, electrocoagulation or radiation. About 12 months later metastatic nodules appeared in the groins.

The diagnosis may be suspected from hearing a characteristic story but it must be proved by microscopic examination. The great majority are squamous carcinoma, grade 2.

The best treatment of the primary tumor is prompt, wide surgical excision. When the inguinal nodes are involved radical groin dissections should be performed. Owing to certain characteristics of squamous cancers, if the patient can be closely observed it appears safe to await microscopic verification of groin metastases before performing inguinal dissections.

Of the 27 patients 11 had no demonstrable metastases when first examined; 4 of this group are alive 5 or more years after treatment. Sixteen patients had metastases when first examined; of these only 2 are living 5 or more years after treatment.

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THE SIGNIFICANCE OF GONADOTROPIC HORMONES IN THE URINE OF PATIENTS WITH TESTICULAR TUMORS

VINCENT VERMOOTEN AND WILLIAM F. HETTLER

In recent years there has been a tendency on the part of urologists to have fewer and fewer biological assays made when they suspect a patient of having a testicular tumor, or to follow the patient's progress after removing a testicular tumor. The chief reason is that so frequently there seems to be no connection between the laboratory reports and the clinical status of the patient.

Patients with obvious testicular tumors may have a "negative prolan" and after operation and deep x-ray therapy develop a strongly "positive prolan" determination. The contradictory reports soon become so numerous that the test is discarded as useless. Our personal experience is not unlike that of many other urologists.

Zondek first used the term "prolan" to describe the gonadotropic hormones found in human pregnancy urine. He called the follicle stimulating hormone "prolan A" and the luteinizing hormone "prolan B." It is now known that the gonadotropic principle found in the urine during pregnancy differs from the gonadotropic substance of the anterior pituitary. The term "prolan" is therefore a misnomer and should no longer be used.

In 1930 Zondek was the first to report an increased excretion of "prolan A" in urine of patients suffering from teratoma testis and in 1931 Ferguson et al. reported the disappearance of "prolan" after irradiation from patients who had had testicular tumors. Later Ferguson classified testicular tumors according to the number of "mouse units of prolan" per liter of urine.

In 1935 Cutler and Owen reported their experiences in 66 cases of teratoma testis and stated that "the evidence supports the view that patients suffering from teratoma testis excrete above 50 mouse units of prolan A per liter of urine, giving to this test a diagnostic value." In the same article they presented a modification of Doisy and Katzman's benzoic acid method. They believed that their method was a more accurate one.

As this became more commonly used in the diagnosis of testicular tumors it was found that in many instances the test was grossly inaccurate—so, like Zondek's term "prolan" the test went into the discard.

Between 1942 and 1945, we had the unusual opportunity of seeing and being able to follow 71 patients with malignant tumors of the testes. Forty-two of these patients had "prolan" determinations made according to a technique similar to that described by Cutler and Owen. One hundred fifty-one determinations were made.

TECHNIQUE

The 24 hour urine specimens were collected fresh, kept at ice box temperature and filtered while cold. To a measured volume (40 cc), five volumes (200 cc) of chilled 95 per cent ethyl alcohol was added. The suspension was strongly shaken and allowed to stand over night in the ice box. The next day the precipitate was obtained by centrifugation and the supernatant fluid was discarded. The precipitate was drained of all alcohol, washed with ether (ethyl), equal in volume to the original urine sample. After centrifuging the ether-precipitate mixture, the ether was discarded and the precipitate saved and allowed to dry at room temperature. It was then strongly agitated with distilled water to yield a concentration 5 times greater than the original urine volume used for the extraction. The water insoluble residue was discarded and the aqueous solution containing the active principle was used for testing. If it became necessary to delay the test, the concentrated powder was kept at room temperature in a desiccator. Very little loss of activity had been noted from such samples.

THE QUANTITATIVE TEST

Virgin, immature female mice, weighing 6–8 gm. at the beginning of the test were used. (The mice used should not weigh more than 12 gm. at the completion of the test and it is preferable that they should not be more than 4 weeks old.)

Inoculations of fresh urine and the concentrated extract were made intraperitoneally by using a 1 cc syringe and a 26 gauge needle. The injections were made as shown in table 1.

TABLE 1

MOUSE NO.	
1	0.1 cc fresh urine
2	0.2 cc fresh urine
3	0.4 cc fresh urine
4	0.1 cc of five-fold extract
5	0.2 cc of five-fold extract
6	0.4 cc of five-fold extract

Each mouse received 5 injections within a 48 hour period. At the end of 90 to 100 hours, the mice were autopsied. Gross observations (or the employment of a hand lens) of the tubes and ovaries were made and tabulated.

Positive gross changes in the tube and ovary that may be observed by the use of a hand lens are as follow: (a) Hyperemia and/or edema of the tube; (b) formation of corpora hemorrhagica; (c) formation of corpora lutea.

Cutler and Owen attributed (a) and (b) to the presence of prolan A and (c) to the presence of prolan B.

In table 1 it was shown that each mouse received 5 injections, and table 2 shows the total amount of urine injected into each of the 6 mice, and the indicated amount of hormone present if the tubes only were positive. If the ovary was also positive the number of units indicated by that mouse was multiplied by 5, since it is believed that it requires 5 times as much of the hormone to produce a positive ovary (in the mouse) as it requires to produce a positive tube.

One hundred mouse units of prolan A per liter of urine was considered as diagnostic, or as a positive test. If the ovary showed corpora hemorrhagica in addition to the tube being hyperemic or edematous, the total mouse units per liter was multiplied by 5.

The 24 hour output of prolan A was determined on all positive tests by multiplying the urine volume (in terms of liters) by the mouse units per liter.

Using this technique our observations were rather interesting for it was seen that of the 16 patients who had had a proven diagnosis of malignant teratoma testis, 7 had negative "prolan" determinations while 9 had positive tests. Of these 9 there was no change in the amount of "prolan" in two patients despite orchiectomy and deep x-ray therapy. In 4 the "prolan" had increased and in 3 it decreased following treatment.

On the other hand there were 26 who had a proven diagnosis of embryonal carcinoma (seminoma or dysgerminoma). Of these, 14 had negative "prolan" determinations and 12 positive. This, for practical purposes, is not very different from the teratoma series. Of the 12 whose "prolan A" tests were positive, there was no change in 2, there was a definite increase in 2 cases and a decrease in 8.

These observations make a very confusing picture and give one the feeling that this rather elaborate test is of no clinical significance or value. It is also in total disagreement with Ferguson's earlier reports. Four patients who had embryonal carcinomata, for instance, had a negative "prolan" determination before treatment but this became positive toward the end of the treatment and now, 3 years after operation they are still well and free from any clinical evidence of metastases.

TABLE 2

MOUSE NO.	QUANTITY OF URINE INJECTED. (5 INJECTIONS)	PROLAN A (MOUSE UNITS PER LITER OF URINE)
	cc	
1	0.5	2,000
2	1.0	1,000
3	2.0	500
4	2.5 (extract)	400
5	5.0 (extract)	200
6	10.0 (extract)	100

A review of the recent literature on this subject, very little of which has found its way into the urologic journals, offers an adequate explanation of these inconsistent reports and indicates why the term "prolan" should no longer be used.

Evans and his associates were the first to point out that the hormone present in pregnancy urine was different from the hormone present in castrates and in women past the menopause. The hormone found in pregnancy urine was found to be elaborated by the chorionic tissue and is known as chorionic gonadotropic hormone (C.G.H.) and bears no relation to the pituitary. However, the hormone *found in the urine of castrates and of women past the menopause is presumed to* be associated with activity of the anterior lobe of the pituitary and is known as the follicle stimulating hormone (F.S.H.).

These two hormones can be differentiated in a variety of methods. Thus, according to Grollman; "When urine is extracted by tricresol, the F.S.H. is destroyed whereas the chorionic gonadotropin is unaffected."

"The follicle stimulating hormone" (F.S.H.) causes ripening of many or of all the follicles and no corpora lutea are found or are only found with a very high dosage. The "chorionic gonadotropic hormone" (C.G.H.) causes luteinizing theca cells and in small doses no follicle formation. C.G.H. given in a dilution just strong enough to give a positive reaction will cause maturation of one of two large graafian follicles plus ballooning of the uterus with watery fluid. With large doses there may be one or many corpora lutea atretica and sometimes the formation of corpora hemorrhagica" (Twombly).

Further "The bill of the English sparrow in the eclipse plumage of the fall and the winter turns black following the injection of pituitary but is uninfluenced by chorionic gonadotropins. The testis of the dove and the ovary of the pigeon increase in weight when stimulated by equine chorionic or by pituitary gonadotropin but are not affected by human chorionic gonadotropin" (Grollman).

The finding of C.G.H. in the urine of a patient suspected of having a testicular tumor or one who has had a testicular tumor removed would be positive evidence that the patient has a tumor in which chorionic tissue is present (Brewers). Usually this would be considered evidence that the primary tumor was teratomatous but Brewer has shown that this is not necessarily the case. The finding of F.S.H. in the urine in a male suspected of having a testicular tumor may only be evidence of a decreased secretion of androgen with a consequent relative increase of F.S.H. Hamburger says that a low output of male hormone releases the pituitary to put out an increase of F.S.H. This "castration effect" may be caused by destruction of the testis by tumor or by surgical or x-radiation castration. For these reasons therefore, F.S.H. may or may not be an indication of the presence of a testicular tumor.

In interpreting the observations on such a given extract it is necessary to remember that one acts as a synergist on the other. Unless we are aware of this fact we may still misinterpret our findings. If, for instance, we have a patient who, preoperatively, is found to have C.G.H. in the urine he is then operated on and the C.G.H. increases in amount. This may mean that metastases are present and have become active, or it may mean that as a result of the castration we now have an increase in F.S.H. This could act synergestically on the C.G.H. and so give the impression of an increase of C.G.H. whereas, in actual fact, there may be a marked decrease.

When therefore, one realizes the significance and importance of differentiating F.S.H. from the C.G.H. and at the same time bears in mind the synergistic effect on C.G.H. by F.S.H. in "castrate urine" one can readily see why there has been so much confusion in interpreting "prolan" determinations in our series of cases as well as in those of other authors.

CONCLUSION

In conclusion we must remember that the presence of "chorionic gonadotropic hormone" in the urine of a male is an indication of chorionic tumor tissue.. Its decrease means removal or regression of the tumor tissue, its increase may mean spread of the disease or may be the result of an increase of F.S.H. and its synergistic effect.

On the other hand, the presence of "follicle stimulating hormone" in male urine is merely an indication of decreased androgen output or a "castration effect." While the castration effect may be due to destruction of testicular tissue by tumor it may also result from other causes such as castration or irradiation.

SUMMARY

Attention is brought to the fact that the term prolan is a misnomer and should no longer be used.

A large series of "prolan" determinations on urine from patients known to have malignant tumors of the testis are reported and the utter confusion of the results illustrated. The technique used in making these determinations is recorded.

The significance of follicle stimulating hormone and of chorionic gonadotropic hormone in the urine is discussed and the various methods of differentiating these hormones when found in the urine are described.

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3) Sensitization phenomena: Fever and erythematous or morbilliform skin rashes. They appear usually after 8 to 10 days of treatment which suggests they are the result of sensitivity.

4) Toxic action of streptomycin on the eighth cranial nerve: Occasionally during prolonged streptomycin treatment, tinnitus, vertigo, and more rarely, deafness develop, apparently as a result of selective toxic action of streptomycin on this nerve. Unless the circumstances are desperate, streptomycin should be discontinued immediately if these symptoms become evident. Deafness may persist for 6 to 8 weeks after termination of streptomycin.

TABLE 1. *Results of streptomycin therapy in 14 cases of urinary infections classified according to infecting organism*

INFECTING ORGANISM	RESULTS			
	No. of pnts.	Recovered	No effect	Died
Escherichia coli	2	2	0	0
Klebsiella pneumonia	1	1	0	0
B. proteus	4	2	2	0
Pseudomonas aeruginosa	2	2	0	0
Staph. non-hemolytic	1	1	0	0
Para colon	2	2	0	0
Aerobacter aerogenes	1	1	0	0
Staph. aureus hemolytic	1	0	0	1
Totals	14	11	2	1

TABLE 2. *Results of streptomycin therapy in 14 cases of urinary infection classified according to diagnosis*

CLINICAL PATHOLOGICAL DIAGNOSIS	NO. OF PNTS.	URINE CULTURE	
		Neg.	Pos.
Tuberculous pyelonephritis and cystitis	1	1	0
Postoperative cystectomy for bladder cancer	1	1	0
Pyelitis	3	3	0
Renal calculus	1	1	0
Pyelonephritis and cystitis	2	2	0
Pseudomembranous cystitis	1	1	0
Hypertrophy of prostate with diverticula	1	0	1
Carcinoma of bladder	1	0	1
Acute bilateral pyelonephritis and acute hemorrhagic cystitis	1	1	0
Acute prostatitis, acute pyelitis	1	1	0
Urethral stricture, bacteremia	1	0	1
Totals	14	11	3

5) Renal irritation: Number of casts, albumin, and red blood cells are increased.

The amount of streptomycin allocated was limited and, therefore, the use of streptomycin in this small series was confined to diseases in which this drug was proven of value, and which were not affected by other therapeutic agents.

The etiological agent was bacteriologically identified in each case and its sensitivity to streptomycin demonstrated before treatment was started. The one case of bacteremia was the only exception; the patient died before sensitivity of the organism to streptomycin could be established. Two cases, to be discussed in detail, showed dramatic clinical results in spite of repeated sensitivity tests that demonstrated a total lack of inhibition of the identified organism to 300 U and 1,200 U of streptomycin per cc. The remarkable response and benefit obtained in vivo with streptomycin therapy in these 2 cases, in contrast to the total lack of streptomycin inhibition and resistance to the causative organism in vitro cannot be satisfactorily explained. It must be admitted that in the treatment of infections with streptomycin there is frequently no recognizable correlation between the in vitro susceptibility of the causative organism to streptomycin and the clinical response.

Streptomycin, like penicillin, is not subject to action interference by pus, tissue autolysates, or peptones, as in the sulfanomides. Streptomycin is inactivated by cevitamic acid, cysteine, and ketone reagents. The inhibitory action of glucose and certain other sugars was also traced to the production of acid from the sugar by the test organisms. It has been claimed that the drug is more effective if an alkaline reaction is maintained during therapy. The production of an inhibitory acid by the test organism may, in part, explain the ineffective response of streptomycin in vitro. Theoretically, this inhibition may cause or result in a false negative streptomycin sensitivity test.

There are two serious limitations to the successful use of streptomycin: 1) The establishment of free flowing urinary drainage is prerequisite if a satisfactory result is to be obtained. Regardless of the effectiveness of streptomycin, it is needless to state that it will never be a substitute for any indicated surgical procedure. 2) The organisms which are sensitive to streptomycin at the beginning of treatment may rapidly become insensitive to it. Prolonged treatment and the treatment of relapses may, therefore, be unsuccessful. Because streptomycin is a bacteriostatic, and an inhibitor, the treatment should be no less than 6 days. Recent experimental data show that insufficient streptomycin therapy may result in the development of resistant strains of organism. Further, Welsh, Price, and Randall demonstrated an increased fatality rate in white mice. Their reported experiments indicate that at certain concentration levels, streptomycin exerts a stimulating effect on certain organisms against which the antibiotic action of streptomycin is directed. If this holds true in man, the proper dosage is an important factor; a difference between failure and success.

In this series, sporadic streptomycin estimations of serum ranged between 10.8 units and 17 units of streptomycin per cubic centimeter when 0.4 gm. of streptomycin was administered every 4 hours. Bioassay determinations of the units of streptomycin in the urine were not carried out.

Approximately three-quarters of the patients in this group responded to streptomycin with urines that became microscopically and culturally negative. Greey found that 4 hours after initiation of streptomycin therapy (1 gm. streptomycin daily, in 8 divided doses intramuscularly), urinary cultures were negative for Proteus vulgaris and after 8 hours, negative for coliform organisms. In this group the average duration of therapy required to bring about a culturally negative urine was approximately 3 days. Hourly and daily cultures were not made and, therefore, the time interval in this series cannot be considered accurate.

The causative organism persisted in the urine in 21.5 per cent of the cases treated. This occurred in the cases complicated by urinary obstruction and stasis.

CASES

Case 7, L. U., aged 26, No. 171863, was seen on July 11, 1946. The patient entered the Veterans Hospital at Hines, Illinois, complaining of severe bladder spasms, strangury, with pus, blood, and debris in the urine, frequency and urgency every 5–15 minutes.

Physical examination revealed a well-developed, well-nourished, white male, with a suprapubic drainage tube in place. Examination by systems was negative.

X-ray of the chest was normal. The urinalysis revealed 2 plus albumin, alkaline in reaction, moderate number of white and red blood cells, and many bacteria. Cultures of the urine revealed an organism of the Proteus species. Streptomycin sensitivity tests: 300 units per cubic centimeters of streptomycin did not inhibit the growth of B. proteus. The blood serology was negative. The blood counts were within normal limits, and the nonprotein nitrogen was 24.1 mg. per 100 cc and ranged to 28.6 mg. per 100 cc.

Intravenous pyelography was normal except for a slight dilatation of the distal end of the right ureter. Cystoscopy established a diagnosis of pesudomembranous cystitis.

Immediately sulfa and penicillin therapy was instituted without any clinical improvement. Bladder irrigations failed and the urine cultures persistently showed an organism of Proteus species.

On August 31, streptomycin therapy was begun and a total dose of 10.5 gm. was administered in 0.4 gm. doses every 4 hours. After the second day of treatment the patient presented marked clinical improvement. Prior to streptomycin therapy the patient had a very intolerant, small capacity bladder (about 75 cc) with marked frequency (every 5–15 minutes), associated with intermittent bladder spasms and marked urgency. Bladder capacity increased, and bladder spasms, urgency, and frequency ceased. The cloudy urine, "flaky shreds", and bacteriuria disappeared, and the urine became clear and normal. The patient was discharged on September 11, 1946 after repeated negative urine cultures.

The response to streptomycin in this case was considered unusual because the streptomycin sensitivity was first erroneously reported as showing "300 units of streptomycin per cc inhibits the growth of B. proteus." A request was made for streptomycin which was granted, and treatment was instituted. On the second day the clinical improvement was dramatic, and on this same day, the laboratory report came to the office reading, "300 units of streptomycin per cc does not inhibit the Proteus species." This fact with the remarkable recovery of the patient was made known to the laboratory No reason was postulated and the phenomenal behavior was not explained.

I believe this case shows conclusively that streptomycin should be given in serious cases where all other methods of treatment have failed even though laboratory tests reveal the organism is not sensitive to streptomycin

The results in case 7 led to the treatment and dramatic cure of the following case in spite of repeated laboratory tests that demonstrated lack of inhibition of streptomycin to the causative organism This organism was resistant to 1200 units of streptomycin per cubic centimeter

Case 13, C W, aged 20, No 172 920, was seen on July 30, 1946 The patient was perfectly well until 5 months before admission when he noticed he became easily fatigued, lost 40 pounds in weight, and began having blood and pus in his urine *Shortly thereafter he developed bladder spasms, strangury,* urgency, and frequency He was hospitalized at the Veterans Hospital, Marion, Illinois from May 21, 1946 to July 26, 1946 He was treated with penicillin, sulfa drugs, and bladder irrigations The patient's condition remained refractory to treatment, and he was transferred to Veterans Hospital, Hines, Illinois on July 30, 1946 with a tentative diagnosis of interstitial cystitis

The patient appeared chronically ill Temperature was 101F, pulse 80, and respiration 18 per minute Examination by systems was essentially negative

The urine was cloudy and contained many red blood cells and clumped white blood cells per high power field, with large amounts of debris, specific gravity varied between 1 010 to 1 012, alkaline in reaction, albumin 4 plus, sugar negative The red blood count and hemoglobin were normal, the white blood count was 13,800 with 82 per cent polymorphonuclear leukocytes The Kahn test was negative The bladder urine contained numerous pus cells, yeast cells, and organism of a para colon species A para colon organism was cultured and found in the urine on August 23, 26, and 27 Urine cultures for fungus on August 16 and 20 revealed no growth Daily negative acid fast cultures and smears were obtained from August 5 to 10 The guinea pig inoculations also were negative The sedimentation index was 27 mm , the nonprotein nitrogen was 30 5 mg per 100 cc

Intravenous pyelography on July 31 showed ill defined kidney outlines The dye appeared in 60 minutes The pelves were not distinctly visualized The calyces were dilated and mottled A diagnosis of pyelonephritis, bilateral, with impaired kidney function was made (fig 1, A) In the 30 minute film, taken September 6, both kidneys had increased in size with definite dilatation of the pelves and calyces (fig 1, *B*) Cystoscopy on August 10, under sodium pentothal anesthesia, revealed a very intolerant bladder, and a diagnosis of acute, hemorrhagic cystitis and acute pyelonephritis was made

The patient was rapidly going downhill and the prognosis was poor Temperature ranged from 100 to 105F On August 5 a therapeutic test of 9 gm of streptomycin in divided doses of 0 4 gm every 4 hours was given Immediately following the first day of treatment the bleeding stopped, the extremely severe, frequent, and painful bladder spasms decreased in number, and the patient's general condition rapidly improved Urine cultures after the first 9 gm of strep-

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ARREST OF URINARY TRACT TUBERCULOSIS DURING PREGNANCY BY STREPTOMYCIN THERAPY[1]

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A 30 year old woman first was seen by us in April 1943. She complained of having had mild irritative bladder symptoms for 1 year. Two weeks previously she had been delivered of a living male infant by cesarian section. The patient was a rather emaciated, chronically ill woman with slight tenderness in both costovertebral angles, and a healing lower abdominal incision. The white blood count was 7500. Urinalysis showed a mixed infection. Urine recovered by ureteral catheterization revealed a positive smear for acid fast bacilli from the right kidney, and subsequent guinea pig inoculation showed bilateral tuberculous infection. The left pyelogram appeared normal. The chest x-ray revealed minimal bilateral apical tuberculous lesions of questionable activity.

A right nephrectomy was performed on May 14, 1943; and tissue studies showed far advanced tuberculosis with extensive caseation. The postoperative course was uneventful and she was transferred to a sanatorium. During her stay there she experienced marked relief from the irritative bladder symptoms but culture of the bladder urine in February 1944 was positive for tubercle bacilli and again positive when she returned for checkup in April 1944. The left pyelograms revealed that a 1 plus hydronephrosis was present. Cystoscopic examination in November 1944 showed a contracted bladder with moderate tuberculous cystitis; but the left ureter could not be catheterized. Intravenous pyelograms showed a slight increase in the hydronephrosis. Cultures for acid fast remained positive through November 1945, at which time pyelograms revealed progressive increase in the left hydronephrosis and cutaneous ureterostomy was advised.

The patient refused this procedure and did not return for nearly 2 years when she was referred back to the urological service from obstetrics because she was 5 months pregnant and the question regarding interruption of the pregnancy had been raised.

During the 1945–1947 interval she had been at home allowing herself moderate activity, but continuing to have urinary frequency of every 2 hours. Since the beginning of this pregnancy the frequency had increased to every ½ hour and was accompanied by dysuria. Intravenous pyelograms revealed the hydronephrosis to be about the same as in 1945. The bladder urine was still positive for tuberculosis.

It was our opinion that streptomycin therapy might offer some hope of controlling the tuberculosis and thus permit a safer continuation of her pregnancy to its normal conclusion. Streptomycin therapy was begun on April 28, 1947, and 2 gm. per day in 5 divided doses with accompanying alkalinization was given. This was continued for a period of 96 days; for a total dose of 192 gm. of streptomycin. During this period, intravenous pyelograms did not reveal any increase in the hydronephrosis and the blood nonprotein nitrogen remained normal.

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[1] Read at annual meeting, North Central Section, Cleveland, O., October 23–25, 1947.

Guinea pig inoculation of urine taken 2 days after establishment of therapy was positive but after 17 days was negative and has remained negative since. The frequency and dysuria decreased rapidly and with the exception of marked vertigo, nausea and vomiting between the twentieth and thirtieth days, there were no apparent untoward effects to either mother or fetus.

Therapy was discontinued on August 2, 1947, and on August 15, cesarian section was performed with the delivery of a normal living female infant. Postoperatively her course was uneventful and when discharged 13 days later, the cesarian wound had healed, the urine showed a mild bacillary infection for which she was given sulfa, but she was free from irritative bladder symptoms and was voiding normally.

Check-up 6 weeks later showed the urine to be still infected, but no acid fast organisms present. Pyelograms revealed a slight diminution in the degree of hydronephrosis on the left and the ureter still showed moderate dilatation along its entire course due to constriction at the ureterovesical junction. Whether or not cutaneous ureterostomy will be the eventual outcome cannot yet be determined.

It has been observed by some pathologists that apparently there is an even greater tendency toward cicatrization following streptomycin therapy than has been observed in the healing of tuberculous lesions before such therapy. One other patient treated with streptomycin in the University of Michigan Hospital who had hydronephrosis and hydroureter from tuberculous cystitis has had a complete remission of the tuberculosis for over 1½ years but had no regression of the obstruction at the bladder level and required cutaneous ureterostomy. It is possible therefore that the healing process of tuberculous lesions when influenced by streptomycin therapy may occasionally follow unfamiliar pathological patterns and produce types of sequellae which have heretofore not usually been observed by phthisiologists.

While the follow-up in the present case is not sufficiently long to determine the permanency of its arrest, the use of streptomycin for tuberculosis of the urinary tract permitted this woman to go through a pregnancy in greater safety and comfort and to deliver a normal living infant.

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PAPAVERINE: ITS VALUE AS AN ANTISPASMODIC IN UROLOGY[1]

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In urology there has always been an urgent need for an efficient antispasmodic. None of the innumerable antispasmodics fulfils the purpose to the complete satisfaction of the urologist. In this paper I should like to call attention to an antispasmodic which I have been using for the past 17 years, and with which I have obtained remarkably good results. It is papaverine.

Papaverine was discovered 1848 by George Merck. It is one of the crystalline alkaloids of opium. It, with narcotine and narceine, is a member of the isoquinoline group, whereas morphine, codeine and thebaine comprise the phenanthrene group. The antagonistic action of these two groups upon the tone of smooth muscles, especially that of morphine and papaverine, has been thoroughly investigated pharmacologically. As far back as 1902, and later in 1913, Pal demonstrated the specific selective relaxing action of papaverine on the tone of smooth muscles. This action is especially pronounced on the pathologically increased tone of smooth muscle, on which morphine exerts a marked stimulating effect. Pal's experiments were especially related to the smooth muscle mechanism of the circulatory system and the digestive tract. Later he also included the urinary tract in the field of papaverine research. He also found that compared with other opiates, papaverine has the least narcotic effect. Many other investigators (O. Schwartz, Grossmann, Hopkins, Gruber) studied the pharmacological and clinical action of this drug, and all confirmed Pal's observations.

The clinical evaluation of the antispasmodic effect of papaverine, however, was restricted to the circulatory system, and, on a smaller scale, to the gastro-intestinal tract. Angina pectoris, thrombophlebitis, spastic peripheral vascular conditions, migraine and Raynaud's disease have been extensively treated with papaverine.

Not much consideration, however, was given to the clinical evaluation of papaverine in spastic conditions of the genito-urinary tract until 1916 when D. Macht reported his studies with papaverine on the tonicity of the ureter. Following this Geraghty and Macht introduced a 2 per cent solution of papaverine directly into a human ureter in which a stone was impacted: the ureter dilated considerably and the stone passed. Macht reliably proved by his extremely interesting experiments that morphine increases the tone and the peristalsis of the ureter, whereas papaverine first depresses than gradually stops peristalsis. The rate and strength of the contractions decrease, and the ureter dilates. H. H. Young with D. Macht also demonstrated the relaxing action of papaverine on the trigonal muscle. Samaan also demonstrated clinical evidence of the therapeutic value of papaverine by direct application, i.e. the spontaneous passing of calculi following ureteral injection.

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[1] Read before New England Section, American Urological Association, at annual meeting, Boston, November 14, 1946.

In all these experiments the drug was applied directly at the site of action. The reason why papaverine has not become a more widely used antispasmodic in urology is that a single dose is readily destroyed once it enters the system. This is especially true when administered by mouth. There is no objection to its intravenous or hypodermic use, but when given in this manner the action is too prompt and of too short duration. Pharmacological studies, however, have shown that papaverine is readily absorbed by the rectal mucosa and at a rate which allows a continuous effect. In a suppository it can be given in fairly large doses without causing any untoward effects. Furthermore, this is an easy means of self administration.

The action of papaverine differs from that of morphine in that papaverine relieves spasm in the urinary tract while morphine increases it. Both will alleviate pain but papaverine is a more effective analgesic because of its antispasmodic action.

Another observation which I should like to mention, and one which would seem further to support the evidence that papaverine acts as an antispasmodic in the urinary tract, is that intravenous urograms show denser shadows of the kidney pelves and ureters after the administration of papaverine. It has also been noted that the kidney pelves and ureters fill more completely, as compared with previous films, after papaverine has been given. Further studies will be necessary to establish these as constant findings.

The uses of papaverine in urology are manifold and it is indicated wherever a spastic condition exists.

In acute distress it may be given intramuscularly or intravenously, but after one injection it is best to continue medication with suppositories in order to maintain prolonged action.

In the acute colic caused by renal or ureteral calculi an intramuscular injection of 100 mg. papaverine hydrochloride may be given. If this fails to give relief it may be repeated in half an hour. In order to keep the hollow system relaxed, suppositories containing 125 mg. for the patient of average weight should be used at 2 hour intervals until relief is obtained. Not more than 5 suppositories should be given.

In the quiet phase of a ureteral stone of suitable size satisfactory results have been obtained; i.e., the stone has passed spontaneously with the following regimen:

The patient is instructed to insert a 125 mg. papaverine suppository every hour for 4 hours, a total of 5 suppositories.

Fluids should be forced (1 quart every hour for 4 hours).

This plan can be carried out without interfering with the patient's daily duties, once or twice a week. It may be repeated at 3 or 4 day intervals for a period of 3 or 4 weeks, unless the condition of the kidney demands prompt relief of the obstruction.

Occasionally a patient may complain of lassitude and throat dryness.

Painful bladder spasms resulting from the presence of a suprapubic tube, pack or hemostatic bag respond well to 125 mg. papaverine suppositories given every 3 hours, if necessary, for several days. The same is true of the painful tenesmus due to acute and chronic cystitis, tuberculous cystitis and acute posterior urethritis.

The painful spastic reaction often following retrograde pyelography or other instrumentation of the ureter is also well controlled by the insertion of one or two suppositories.

Painful priapism and Peyronie's disease, with painful erections, are further indications for papaverine treatment. As a preventive measure against painful erections after any operation on the penis (e.g. urethrotomy, repair of hypo- and epispadias, circumcision, etc.), papaverine is, in my opinion, the drug of choice.

These are briefly the features of papaverine treatment in urology with its indications and technical details. The results are gratifying. As in any other field of medication we occasionally encounter papaverine resistant cases. Nevertheless, we ought to consider papaverine as a valuable drug in our urological medical armamentarium.

370 Commonwealth Ave., Boston 15, Mass.

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A NEW CYSTOSCOPE AND ITS CLINICAL USES

THOMAS J. KIRWIN

From the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital, New York, N. Y., and New York City Hospital, New York, N. Y.

In the February 1946 *Journal of Urology*, I described a new cystoscope, which embodies several principles of construction never before employed in such an instrument. I prefaced my description with a short sketch of the history of cystoscope making, showing how step by step the instruments in general use today have been evolved from the crude beginnings of Nitze and Leiter, though always maintaining certain basic principles envisaged by these pioneers. This review showed how greatly the urologic patient of today has benefited by the modifications, improvements and additions of more than 70 years, and how much the wide employment of cystoscopes so modified has contributed toward making urologic diagnosis the most scientifically accurate investigation of disease available to any medical specialty.

The new instrument I am offering I believe is an advance over anything that has gone before. It offers many advantages which every cystoscopist will immediately appreciate. I will restate the special features of the instrument which I am about to present.

1. The optical system embodies a new lens design for a right angle system and affords a larger field of vision carefully corrected for chromatic and spherical aberration. All of the lenses are coated by high vacuum deposition process with a quarter wave length thickness of magnesium fluoride. This coating decreases loss of light by reflection on each air glass surface and eliminates shadows, flare, and ghost images. Reduction of loss of light by reflection results in an increase in the amount of light transmitted through the optical system by as much as 150 per cent. The image produced is clear and sharp and fine details of structure are distinctly outlined.

2. The flexible beak facilitates introduction of the cystoscope into the urethra, particularly in cases where an enlarged median lobe of the prostate is encountered. Withdrawal of the instrument is simplified because the flexible beak follows the contour of the prostatic urethra. Flexibility of the beak permits use of the instrument as an endoscope.

3. A double fenestra enables the examiner to view both sides of the bladder or urethra without changing the position of the sheath, lessening the danger of trauma and obviating annoyance to the patient. The telescope rotates a full 180° to either fenestra opening by depressing a small release lock.

4. The water inlets and outlets have been substantially increased in size to permit a more rapid flow of water for filling and emptying the bladder, thereby permitting easier and quicker manipulation and shortening the examination.

5. The stopcock has been modified to simplify control of water inlet and outlet. This is accomplished by pressing a conveniently located button on the top of the stopcock.

6. An improved bayonet type of lock actuated by a knurled lever assures a

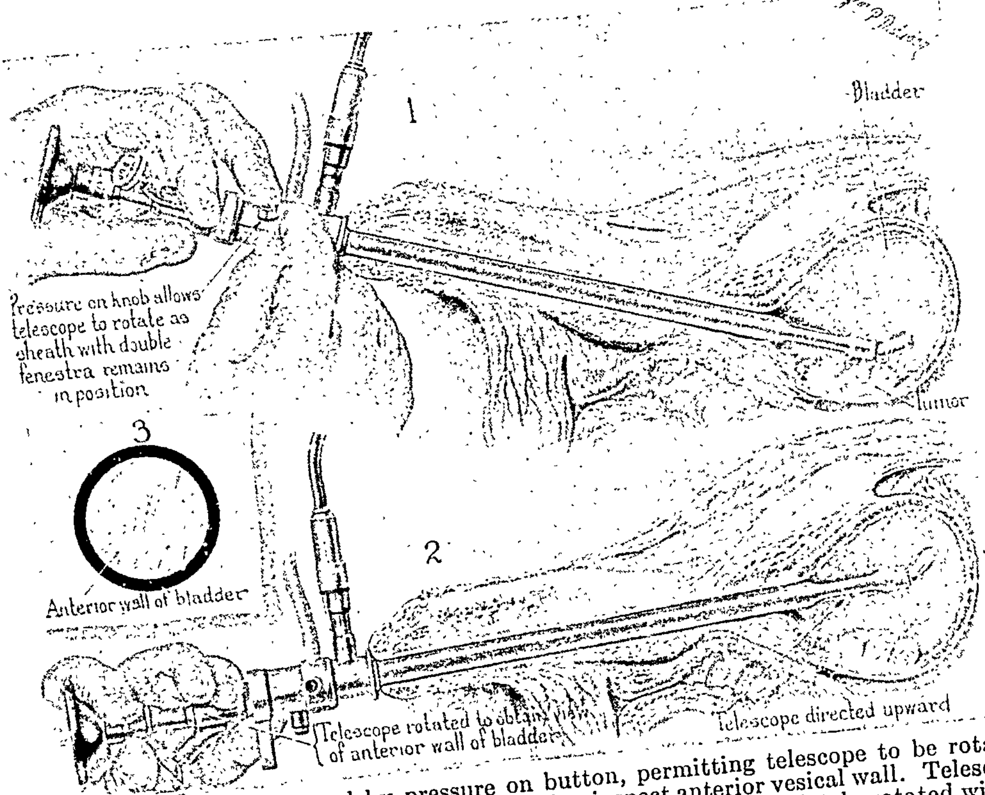

Wm P Didusch
1
Bladder
Pressure on knob allows telescope to rotate as sheath with double fenestra remains in position
Tumor
3
Anterior wall of bladder
2
Telescope rotated to obtain view of anterior wall of bladder
Telescope directed upward

FIG. 4. *1*, Lock is released by pressure on button, permitting telescope to be rotated within sheath so that double fenestra can be used to inspect anterior vesical wall. Telescope is partly rotated while sheath remains stationary. *2*, Telescope completely rotated within sheath; lens is now directed toward anterior bladder wall. *3*, Anterior vesical wall as seen through the cystoscope.

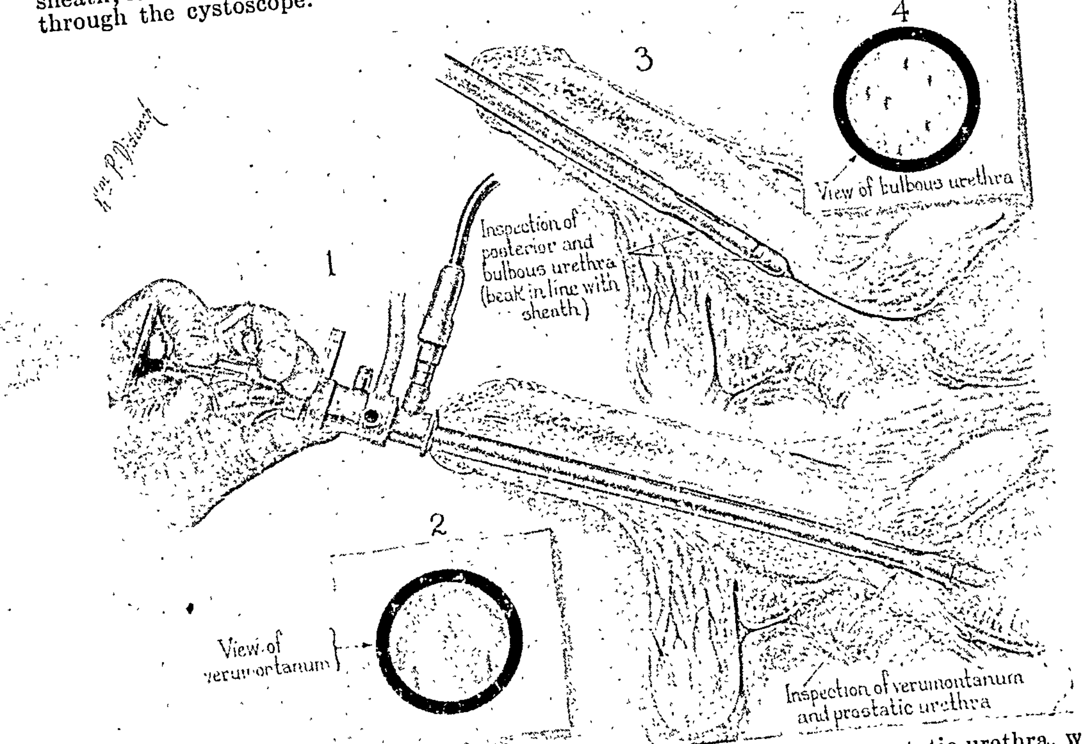
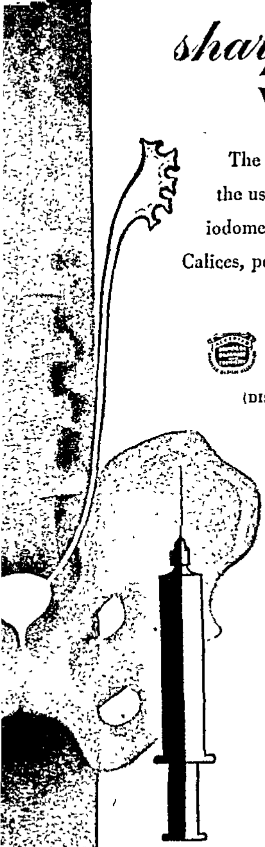

4
3
Wm P Didusch
View of bulbous urethra
Inspection of posterior and bulbous urethra (beak in line with sheath)
1
2
View of verumontanum
Inspection of verumontanum and prostatic urethra

FIG. 5. Use of instrument as a urethroscope. *1*, Instrument in prostatic urethra, with lens directed toward verumontanum. *2*, View of verumontanum seen through cystoscope. *3*, Instrument in use to examine bulbous and posterior urethra. *4*, Cystoscopic view of bulbous urethra and small duct openings.



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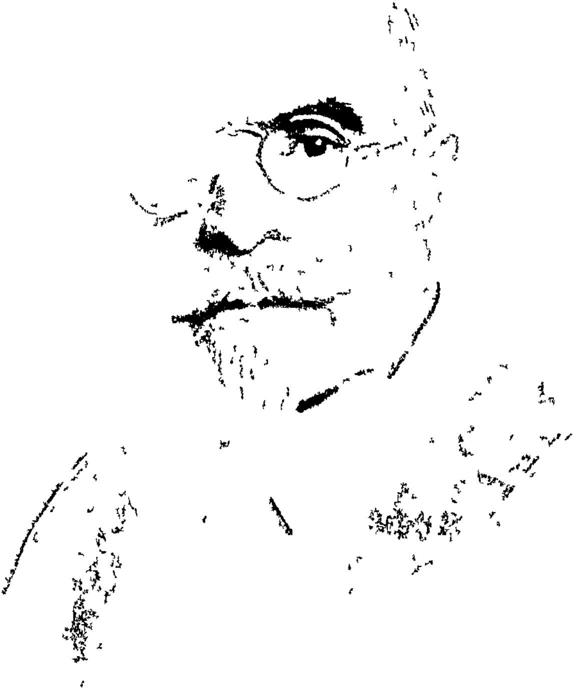

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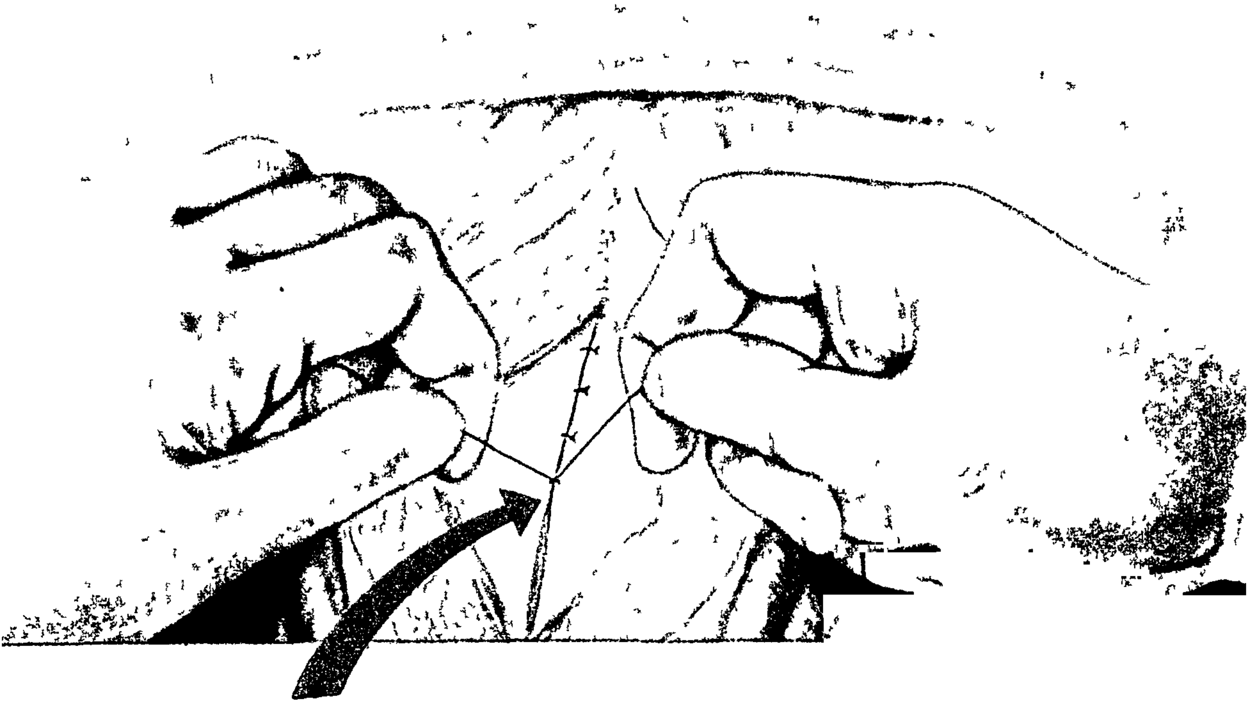

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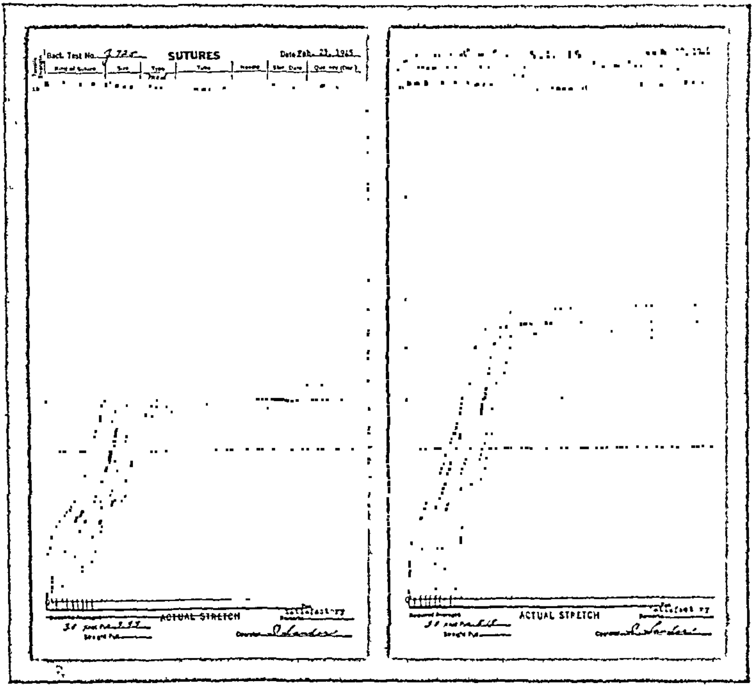

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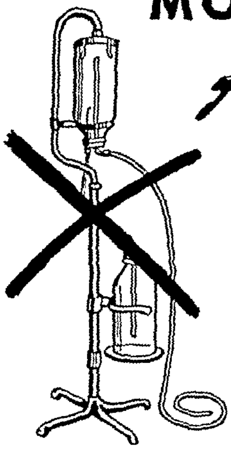

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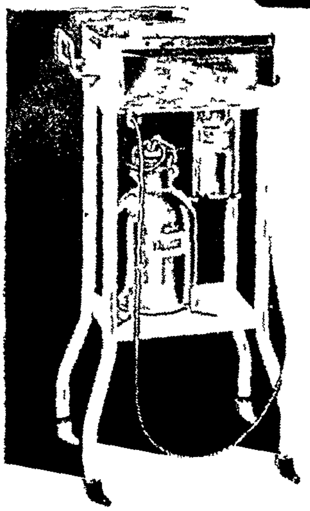

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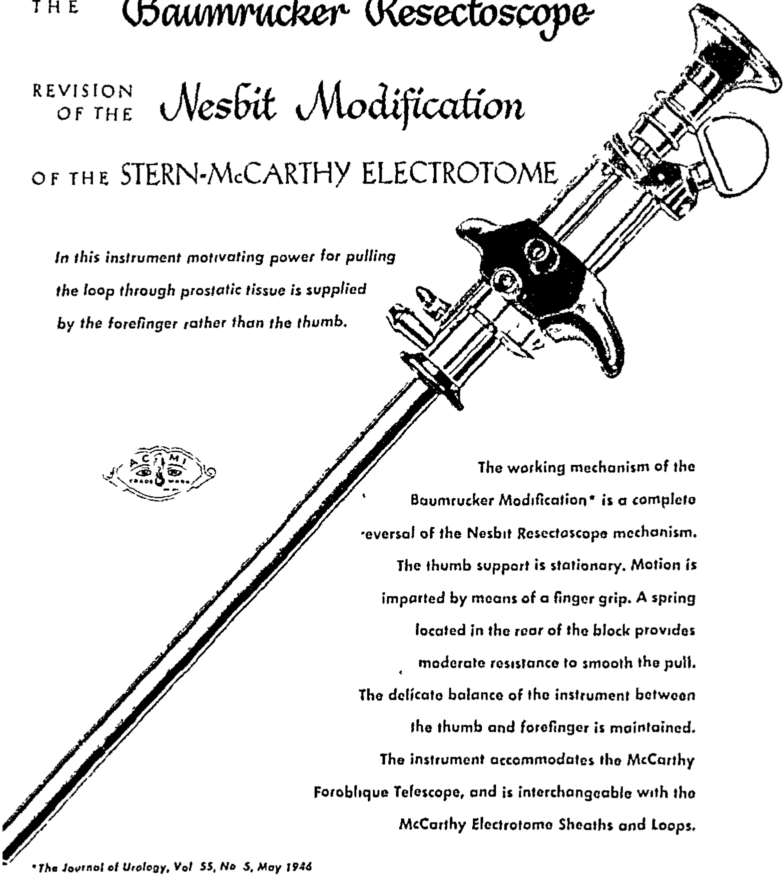

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*The Journal of Urology, Vol 55, No 5, May 1946

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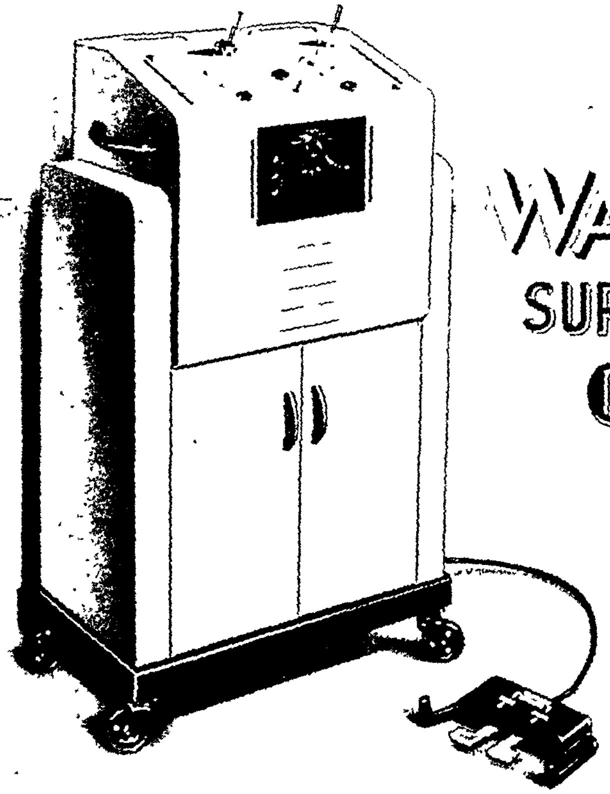

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THE PHYSIOLOGY OF THE INTACT HUMAN URETER[1] [2]

JACK LAPIDES

From the Department of Surgery, University of Michigan, Ann Arbor

Extensive research has been conducted on the physiology of the ureter but many problems remain Some of the most important questions, still remaining definitely unanswered, involve the neuro-anatomy and neurophysiology of the ureter Engelmann[3] in 1869 demonstrated that there were no ganglia in the muscular or mucosal layers of the ureter but he did find a few ganglia in the adventitial layers of the renal and vesical ends of the ureter On the basis of his research he postulated that normal ureteral peristalsis was myogenic in origin He also observed that there was a nerve supply to the ureter but did not know its exact role The distribution of the ganglia in the adventitial layer of the ureter was substantiated by Hryntschak[4] in 1925 Opposing the findings of Engelmann and Hryntschak are the observations of Satani,[5] Dogiel,[6] Maier[7] and many others, that there are ganglia throughout the adventitia of the ureter as well as some in the submucosa and between the muscle layers of the ureter Nicotine has been utilized by some investigators to determine the presence of ganglia but their work has not been completely accepted [8]

There are several schools of thought regarding the origin and mechanism of ureteral contractions Andler,[9] Budge[10] and Valentin[11] postulated that impulses from the central nervous system were necessary for the production and maintenance of ureteral peristaltic waves Maier,[7] Engelmann,[3] Wharton,[12] Satani,[5] Wu,[13] and Hryntschak[4] on the other hand, believed that the ureters can function automatically and initiate their own muscular contractions without the necessity of external neural connections Most workers, Barringer,[14] Wu,[13] Quinby,[15] Satani,[5] Henderson[16] and Robinson[17] are agreed upon the fact that the adequate stimulus for ureteral peristalsis is diuresis or the production of urine by the kidneys They believed that urine pressure, by the degree of distension of the ureteral wall, initiates and influences the peristaltic activity of the ureter Wu[13] and Robinson[17] postulated that the chemical composition of the urine may also play a part. These same workers state that within certain limits the degree of peristaltic activity varies directly with the intraureteral pressure or the diuretic activity of the kidney.

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[1] Read at annual meeting, Am

[2] The Committee on Scientific
B Wesson, chairman, awarded th
in this paper EDITOR

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PURPOSE

This investigation was undertaken in order to determine the normal physiology of the intact ureter in the human. Since it is not feasible to section or stimulate mechanically nerves in the unanesthetized intact human patient, it was decided to accomplish these desired actions by pharmacological means. The problem was studied in four sections.

In the first section general observations were made on the efficacy of the apparatus and on the effect of mechanical stimuli upon ureteral peristalsis. The second section involved observations on the effect of blockade of transmission of nervous impulses on ureteral contractions. The third section concerned itself with the results of stimulation of the sympathetic and parasympathetic nervous systems upon ureteral activity. In the fourth section the effects of drugs reputed to possess either smooth muscle relaxing or stimulating qualities were studied.

METHOD

Patients with apparently normal urinary tracts were selected as subjects. Fluids were forced in most of these patients for 2 hours prior to the start of the experiment in order to insure good diuresis and an approximately constant volume output of urine during the study. The apparatus utilized in recording ureteral activity is a modification of Trattner's original device.[23] Whistle tip ureteral catheters, Nos. 5–8 F. were inserted into the ureters and contractions recorded from various levels. Since optimal ureteral activity was recorded in the lower one-third of the ureter (in accordance with Trattner's findings), catheters were placed in that position in the majority of the patients. After connecting the catheter to the ureterometer, a normal tracing was obtained. Occasionally 2–5 cc physiological saline was injected into the ureter in order to determine the reaction of the ureteral muscle to increased pressure.

In addition to the catheter in the lower one-third of the ureter, another catheter of equal calibre was introduced into the pelvis of the opposite kidney. The purpose of this catheter was to obtain urine samples so that the volume of urine excretion could be followed accurately as a control and to exclude any variables affecting output due to ureteral contractions or artefacts produced by the apparatus. *It is emphasized that an accurate check of urine volume output is of utmost importance in the evaluation of ureteral activity as affected by various drugs; this point will be discussed in detail later in the paper.* In many of the cases a roentgenogram of the KUB region was taken at the close of the experiment in order to verify the positions of the ureteral catheters.

OBSERVATIONS ON THE EFFECTS OF MECHANICAL STIMULI UPON URETERAL CONTRACTIONS

In accordance with observations by Trattner[24] it has been demonstrated that ureteral contractions may vary markedly in rate, rhythm and frequency in different patients as well as in the same subject. Many ureters will maintain the same type of peristaltic wave for periods of an hour or more. Figure 1, A illustrates four different types of contractions occurring in a ureter in a period of less than one half hour. In figure 1, B the ureter is observed to maintain the same type of contraction over a long period of time.

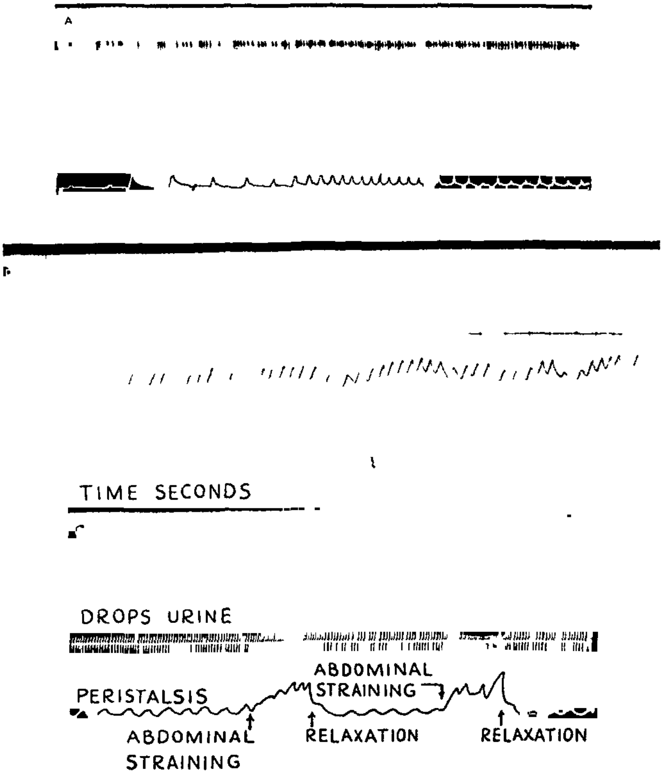

FIG. 1. A Ureter demonstrating 4 different types of contractions in period of less than one half hour. *B, Ureter maintaining same type of activity over long period of time.* Time in seconds is recorded at upper margin of kymograph sheet, ureteral peristalsis at lower border and urine output in drops in area between two. C Illustrating how increased abdominal pressure produced by straining, produces amplitude of peristaltic waves with apparent increase in output of urine per unit time.

Increased abdominal pressure, produced by straining, will produce a marked increase in intraureteral pressure, an increase in frequency and amplitude of the peristaltic waves with an apparent increase in output of urine per unit time; this is well illustrated in figure 1, *C*.

Any increase in resistance to the outflow of urine from the ureter, provided the volume outflow per unit time remains constant, will result in an increase in

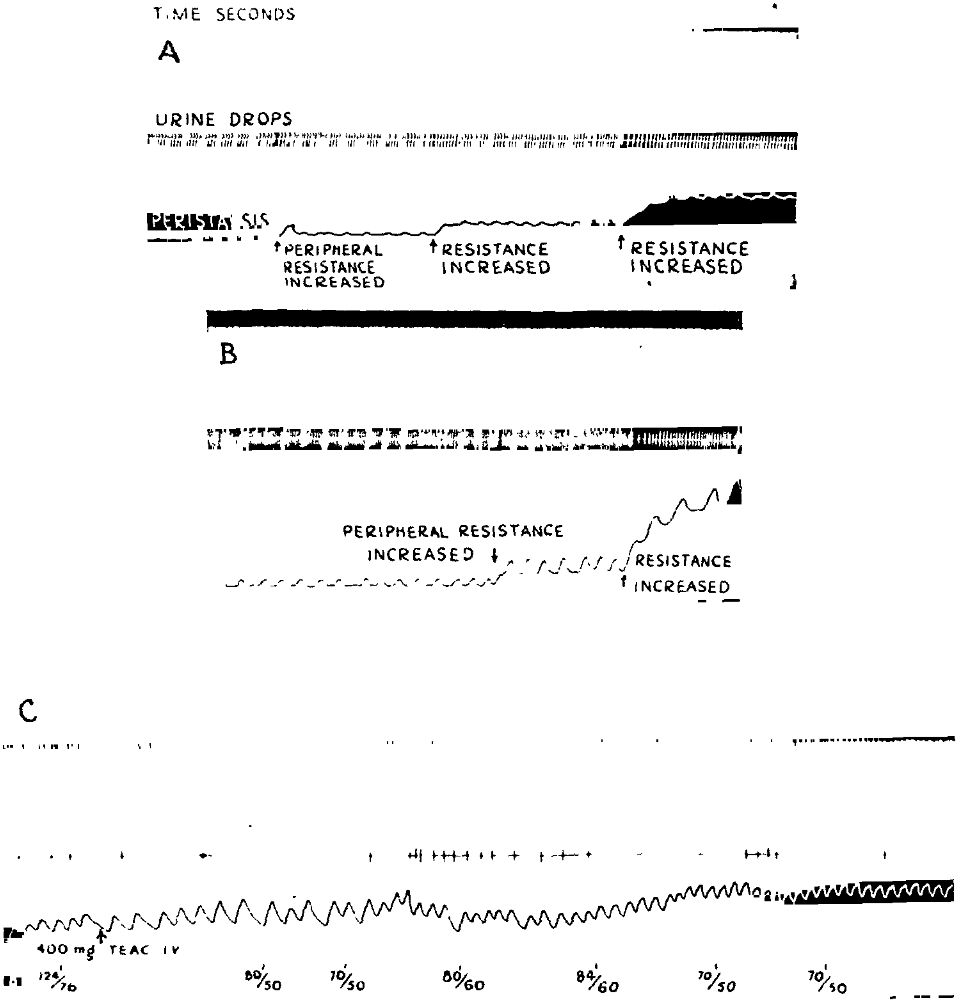

FIG. 2. *A* and *B*, Showing effects of increasing resistance (by decreasing calibre of outflow valve on ureterometric apparatus) on ureteral peristalsis. *C*, Effect of autonomic blockade on ureteral contractions produced by insertion of catheter too large for lumen of ureter.

intra-ureteral tone and peristalsis. The peristaltic waves may increase in frequency or amplitude, frequency *and* amplitude or may demonstrate an increase in frequency with a decrease in amplitude. In figure 2, *A* and *B* can be observed the effects of increasing the resistance (by decreasing the calibre of the outflow valve on the ureterometric apparatus) on ureteral peristalsis. If intra-abdominal pressure and peripheral resistance remain constant, then an increase in volume of urine excreted by the kidneys will result in appropriate changes in ureteral peristalsis. Figure 13 demonstrates the effect of increased urine output on ureteral peristalsis while figure 16 depicts the results of decreased urine output on ureteral contractions. It will be observed in figure 13 that as urine output increased, intraureteral pressure increased and peristaltic contractions increased in amplitude. A further increase in urine output resulted in an increase in frequency and a decrease in amplitude of contractions. On the other hand, figure 16 illustrates the effect of a decreasing urine output on intra ureteral pressure and peristalsis. It will be seen that there is a gradual decrease in intra ureteral pressure with an accompanying decrease in frequency and amplitude of contraction.

It has been observed that the ureteral output as recorded by the ureterometric apparatus does not always bear a relationship to the ureteral contractions, it is believed that abnormal conditions are present when this condition obtains. Some of these abnormal conditions are (a) increased resistance to ureteral outflow occurring in the apparatus due to a partial obstruction, e g, blood clot (b) the use of too small an outlet opening in the apparatus in conjunction with a ureteral catheter that does not fit the ureter snugly enough—thus permitting much of the urine to flow down alongside the catheter into the bladder instead of through the ureterometer and (c) utilization of a catheter which is too large for the ureteral lumen resulting in irritation of the mucosa and stretching of the ureteral muscle with the production of colic and ureteral contractions which bear no relationship to the volume of urine excretion as illustrated in figure 2, *C*.

THE EFFECTS OF BLOCKADE OF THE AUTONOMIC AND SOMATIC NERVES ON URETERAL CONTRACTIONS

The effect of blockade of the autonomic ganglia on ureteral peristalsis. Acheson, Moe and Perera[20, 21, 22] demonstrated that the quaternary ion, tetraethylammonium, produces a blockade of both sympathetic and parasympathetic ganglia. The effects of parenteral administration of the tetraethylammonium ion in man[18, 19] are urinary retention, fall in blood pressure, an increase in heart rate, postural hypotension, increase in peripheral skin temperature, ptosis of the upper eyelids, loss of accommodation, dry mouth and decreased gastro intestinal motility.

Twenty-one patients were given doses of tetraethylammonium chloride varying from 250–400 mg intravenously. A normal tracing was obtained in each patient before the drug was administered. Ureteral peristalsis was recorded during and after the injection of the drug for periods varying from 20–45 minutes. It has been found[19] that the effect of the drug (given intravenously) will begin to disappear within 5 minutes after injection and usually will have vanished within 30 minutes. Blood pressure readings were obtained before and after drug administration.

Blockade of the sympathetic and parasympathetic ganglia by means of the

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[18] Lyons, R. H., Moe, G. K., Campbell, K. N., Neligh, R. B., Hoobler, S. W., Berry, R. L. and Remnich, B. R. Univ. Hosp. Bull. Ann Arbor, 12: 33, 1946.

[19] Nesbit, R. M., Lapides, J., Valk, W. W., Sutler, M., Berry, R. L., Lyons, R. H., Campbell, K. N. and Moe, G. K. J. Urol., 57: 242, 1947.

tetraethylammonium ion produced two types of responses in the peristaltic activity of the intact human ureter. Figure 3, *A* and *B* illustrates the general type response obtaining in 55 per cent of the subjects. It will be noted that the ureteral contractions are not abolished and that there is little change in the frequency, amplitude and rhythm. In these patients TEAC (tetraethylammonium chloride) produced only a slight drop in systolic and diastolic blood pressures although the other responses, e.g., ptosis of the lids, tingling of the extremities and dry mouth were marked; urine volumes were unchanged. Approximately 45 per cent of the patients demonstrated a cessation of peristaltic activity for periods varying from 2–40 minutes after intravenous administration of the tetraethylammonium ion. Inactivity of the ureter was accompanied by diminished urine output and marked decreases in systolic blood pressures ranging from 20–50 millimeters of mercury. Peristalsis ceased for approximately 3 minutes in figure 4, *A* accompanied by a decreased urine output; blood pressure fell from 120 to 90 millimeters mercury systolic pressure. In figure 4, *B* it is seen that peristalsis is absent for a period of 9½ minutes and urine output is decreased; blood pressure dropped from 130/70 to 86/58. The most marked response in this group is illustrated in figure 4, *C*. Peristalsis ceases for a period

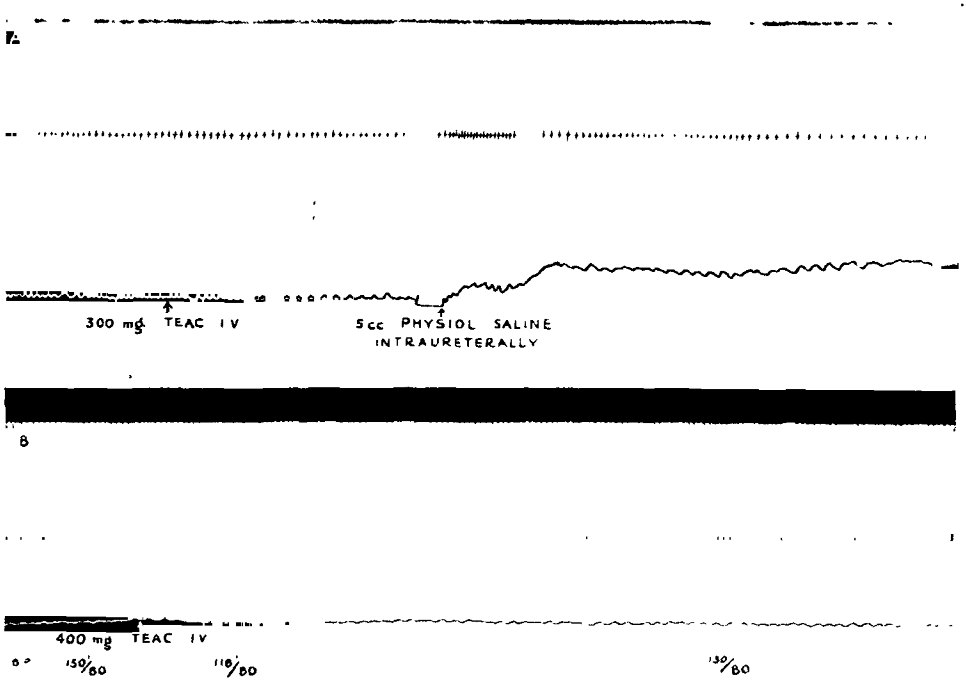

FIG. 3. Response of ureter to tetraethylammonium chloride. *A* and *B* demonstrate little or no change in frequency, amplitude and rhythm of ureteral contractions after autonomic blockade.

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[20] Acheson, G. H. and Moe, G. K.: J. Pharmacol. and Exper. Therap., **84:** 189, 1945.

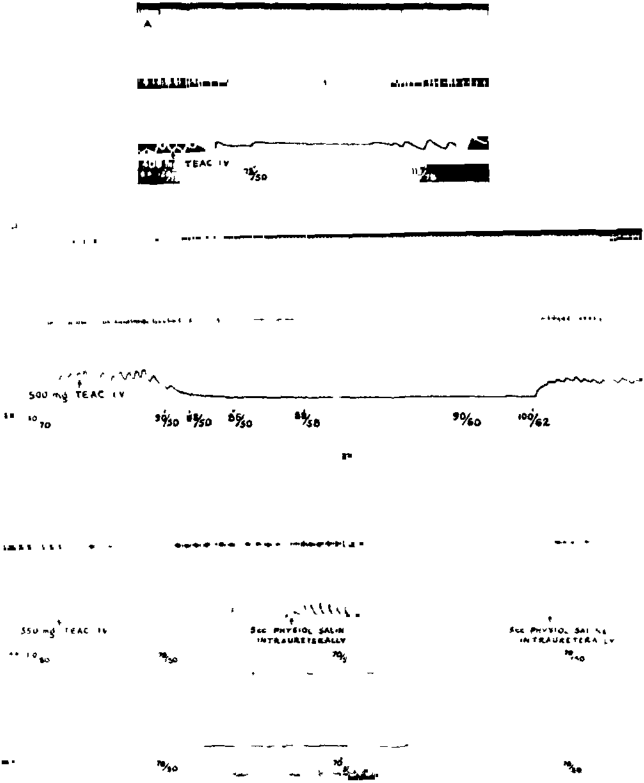
[21] Acheson, G. H. and Pereira, S. A.: J. Pharmacol. and Exper. Therap., **87:** 273, 1946.

[22] Acheson, G. H. and Moe, G. K.: J. Pharmacol. and Exper. Therap., **87:** 220, 1946.

[23] Trattner, H. R.: J. Urol., **11:** 477, 1924.

[24] Trattner, H. R.: J. Urol., **28:** 1, 1932.

of 2¼ minutes and then is resumed for 3 minutes after which it is absent for approximately 40 minutes. Urine output during the 40 minute period of ureteral quiescence was about ½ cc. The patient's blood pressure fell from 114/88 to 70/50 after 350 milligrams of TEAC was given intravenously; this low pressure was maintained throughout the period of ureteral inactivity. It will be noted



d marked hypotensive on. A, Cessation of ...crease in urine output. B, Absence of contractions f... tion to hypotension and decreased urine excretion ... 40 minutes accompanied by relative anuria and ureter ... ...jected into ureter during inactive phase elicited a peristaltic response. Second line from lower margin of record indicates urine output recorded on second run of kymograph drum during last 30 *minutes* of experiment; bottom line is record of ureteral activity during this period.

that peristaltic contractions were elicited during the quiescent period by the injection of 5 cc of physiological saline intraureterally.

Figure 2, *C* demonstrates the effect of TEAC upon ureteral contractions produced by a catheter which was too large for the lumen of the ureter. It will be seen that the contractions were not affected by TEAC even though the urine output was greatly diminished and the blood pressure had dropped from 100/80 to 70/50.

Discussion. It can be postulated, on the basis of the results obtained, that ureteral peristaltic activity is not dependent upon its autonomic nerve supply. Peristalsis appeared to be affected only when there was a marked diminution in urine excretion which in turn bore a direct relationship to the changes in systolic blood pressure. If there was little change in blood pressure, after TEAC administration, diuresis remained unchanged as well as peristalsis. This would seem to indicate that the change in urine excretion obtained with the tetraethylammonium ion is dependent upon the change in systolic blood pressure. It is also apparent that the peristaltic contractions of the ureter bears a direct relationship, within limits, to the volume of urine excreted by the kidneys. When TEAC greatly diminished urine output, peristaltic activity disappeared. That the cessation in peristaltic activity was not due to blockade of autonomic ganglia located in or associated with the nerve supply of the ureter, is indicated by the fact that stimulation of the ureter during its inactive phase by intraureteral injection of physiological saline, elicited peristaltic waves.

Tetraethylammonium chloride has been administered to patients with ureteral and renal colic with no apparent relief. Colic can be produced experimentally by the rapid injection of physiological saline while the patient is under the full effects of the drug.

The effect of high procaine spinal anesthesia on ureteral peristalsis: It has been commonly observed by surgeons that the ureter will continue to contract under deep general anesthesia as well as under spinal anesthesia. Since the ureter is supposedly supplied by nerve fibers from the renal, spermatic or ovarian and the hypogastric plexuses,[8] it was decided to place patients under procaine spinal anesthesia which would be high enough to blockade all impulses traveling down the above-mentioned fibers. Figure 5, *A* demonstrates the effect of spinal anesthesia, extending to spinal segment D4, upon ureteral peristalsis. It will be noted that ureteral peristalsis is quite vigorous despite the inactivation of its total nerve supply. At point R the outlet of the apparatus was closed to observe the reaction of the ureter to increased pressure and it will be seen that the response is normal.

The effect of blockade of the somatic neuromuscular junction on ureteral contractions: Although the ureters are apparently innervated by the autonomic nervous system, it was thought that it would be well to rule out any possibility of somatic nerve supply. Consequently 3 conscious unanesthetized patients were administered curare in the form of Intocostrin intravenously. Curare is an autonomic blocking agent which acts primarily on skeletal muscles and to a lesser degree on autonomic ganglia. It acts directly upon the cell and prevents it from responding to acetylcholine. In pharmacological terms it may be stated that curare paralyzes the nicotinic action of acetylcholine. Ordinarily the full effect of curare on the skeletal musculature is developed long before complete ganglionic blockade is observed. Ureteral peristalsis was not affected in any 1 of the 3 cases. Figure 5, *B* illustrates the reaction of the ureter of a 21 year old patient to the intravenous injection of 120 units of Intocostrin over a period of 5 minutes. All of the skeletal musculature with the exception of the diaphragm was paralyzed. *It will be noted that after the injection of 80 units* of Intocostrin, there was a decrease in intraureteral tension accompanied by a decrease in frequency of peristalsis, a decrease in urine flow and a drop in blood pressure. *Despite the fact that another 40 units were given during this period, it will be observed that peristalsis and intraureteral pressure returned to pre-injection levels.* The transient decrease in ureteral peristalsis following the second dose of Intocostrin was due to the decreased urine secretion brought on by the fall in blood pressure resulting in decreased glomerular filtration pressure (which is not uncommonly seen after intravenous injection of large doses of Intocostrin).

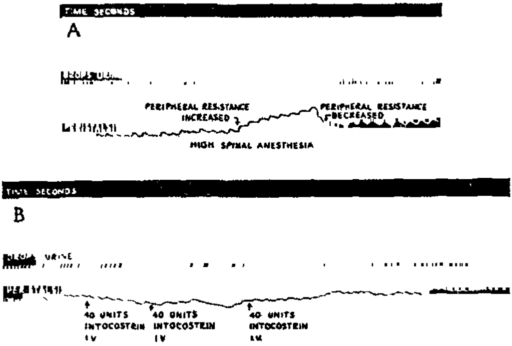


FIG. 5

The effect of blockade of the parasympathetic endings on ureteral activity: Alkaloids of the belladonna group were used in an attempt to paralyze the parasympathetic endings or to inhibit structures innervated by postganglionic cholinergic nerves (paralysis of the muscarine effect of acetycholine). Atropine, a natural drug of this group, and Trasentin, a synthetic drug, were utilized.

Investigators[25, 26] have found that atropine has a variable effect on normal ureteral peristalsis and sometimes a quieting effect on increased peristalsis supposedly due to morphine. These workers made their observations on intact human ureters. It must be emphasized, however, that no accurate check was

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[25] Ockerblad, F. N., Carlson, H. E. and Simon, J. F.: J. Urol., 33: 356, 1935.
[26] Trattner, H. R.: Urol. and Cutan. Rev., 39: 81, 1935.

made on changes in urine output in their experiments, thus leaving their observations highly open to doubt.

Slaughter et al.[27] made observations on the effect of "Trasentin A" on the isolated or excised ureter. They found that it had an antispasmodic effect on the isolated ureters no matter whether the segments were spontaneously contracting or whether they were stimulated by adrenergic cholinergic or "myonergic" drugs.

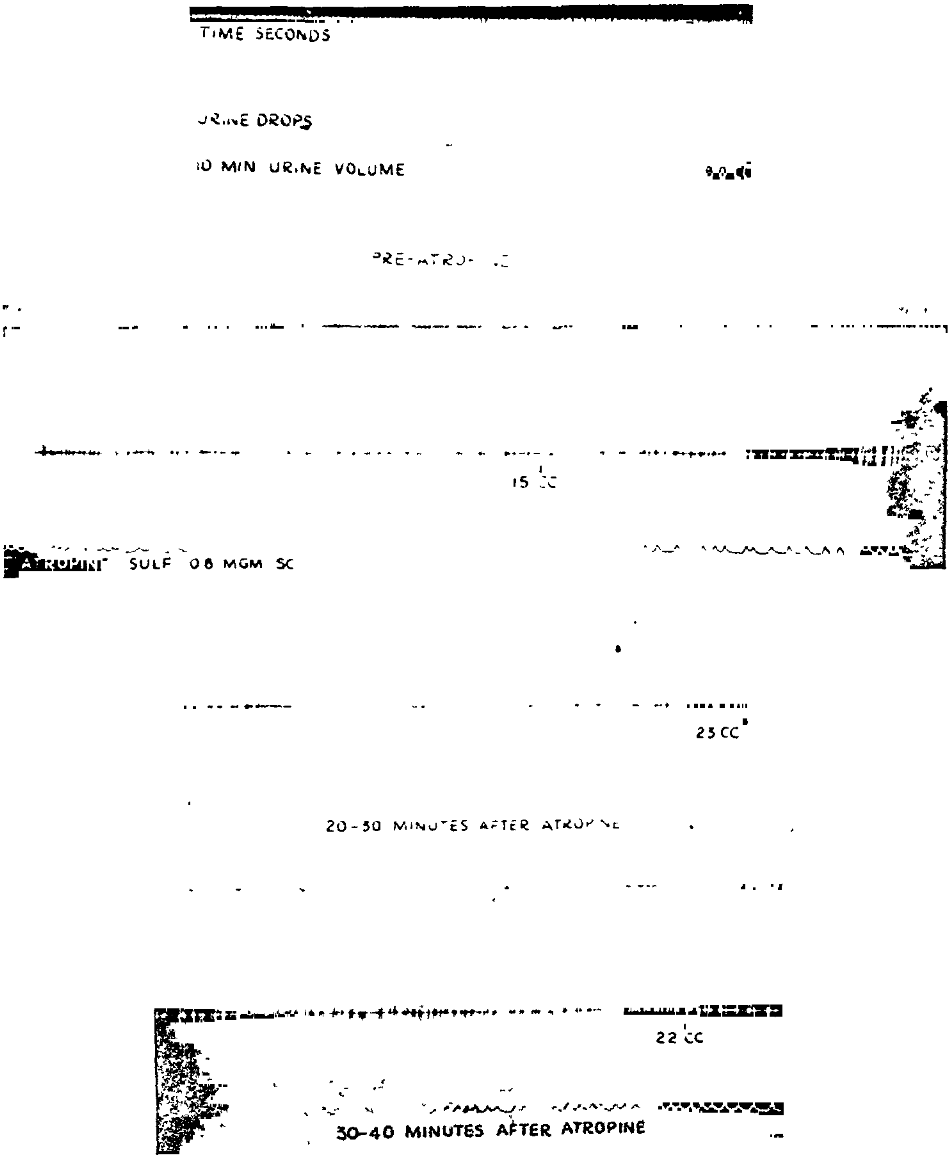

FIG. 6

Ten patients were used in this series of experiments; 5 were given a dose of 0.8 mg. of atropine sulfate subcutaneously and the remaining 5 received 100 mg.

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[27] Slaughter, D., Johnson, T. U., Tobolowsky, N. and Van Duzen, R.: Texas Reports on Biology and Med., 3: 37, 1945.

of Trasentin intramuscularly. In no case was there an observable effect either upon ureteral peristalsis or upon intraureteral pressure. Urine output per unit of time remained approximately constant throughout the duration of each experiment. Figure 6 demonstrates the effect of atropine and figure 7, the effect of Trasentin upon ureteral contractions.

Summary. Chemical blockade of the autonomic nervous system (at the parasympathetic endings (atropine), at both the sympathetic and parasympathetic ganglia (tetraethylammonium ion) and at the level of the spinal cord (procaine high spinal anesthesia)) as well as blockade at the somatic neuromuscular junctions (curare) produced *no* change in ureteral contractions or intraureteral pressure, provided the urine volume output per unit of time and peripheral resistance were kept constant.

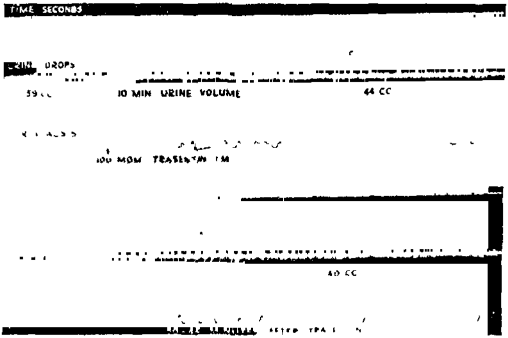

Fig. 7

From the observations made in this section it can be concluded that the ureter is able to carry on peristaltic activity without the aid of extrinsic nerves.

THE EFFECTS OF SYMPATHOMIMETIC AND PARASYMPATHOMIMETIC DRUGS UPON URETERAL CONTRACTIONS

Although it has been demonstrated in the previous section that ureteral peristalsis obtains despite chemical denervation of the extrinsic nerves, it has not been shown whether or not these extrinsic nerves can influence ureteral peristalsis when they are stimulated. In this section the effects of administration of sympathomimetic and parasympathomimetic drugs upon ureteral contractions will be described.

The effect of a sympathomimetic drug upon ureteral peristalsis. In evaluating the results obtained from the parenteral injection of epinephrine hydrochloride in the intact human subject, one must obviously take into consideration the variations in urine output produced by epinephrine. Richards et al.[28, 29] observed in the frog that small amounts of epinephrine will produce an increase

[28] Richards, A. N., Barnwell, J. B. and Bradley R. C.: Am. J. Physiol., 79: 410, 1927.
[29] Richards, A. N. and Schmidt, C. F.: Am. J. Physiol., 71: 178, 1924.

in urine secretion while large amounts of epinephrine will produce a decrease in urine output. They postulated that small amounts of adrenalin caused a constriction of the efferent renal arteriole resulting in a rise in the perfusion or filtration pressure with a consequent increase in urine secretion. On the other hand, large amounts of epinephrine will produce a constriction of both the vasa afferentia and efferentia with a resultant reduction in blood flow through the glomeruli and retardation in or abolition of the secretion of urine. These observations were confirmed by Winton[30] in his studies on the isolated dog's kidney.

Lucas[31] found that epinephrine increased the tone and contractility of ureteral muscle. On the other hand Elliott[32] observed that epinephrine and stimulation of the sympathetic nerves produced no constriction of the ureter in any animal of the various species studied by him.

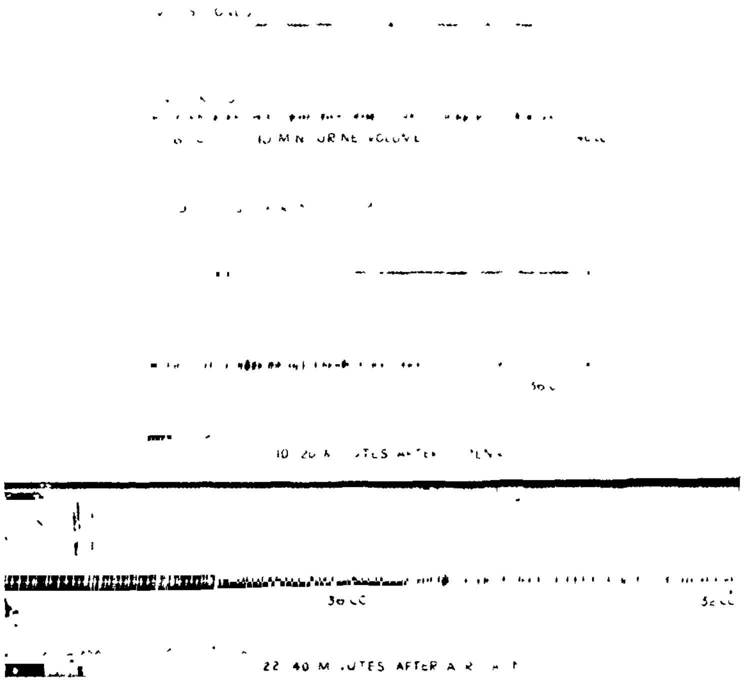

FIG. 8

Observations were conducted on 9 patients some of whom received an intramuscular dose of 0.25 cc. of a 0.1 per cent solution of epinephrine hydrochloride while the other received doses varying from 0.5 to 0.7 cc. of the 0.1 per cent solution. The subjects receiving the small dose of epinephrine exhibited two types of responses namely, no change or an increase in urine output. The ureteral activity corresponded to the changes in urine output. Figure 8 demonstrates no change in ureteral peristalsis or urine output following the injection of epinephrine while figure 9 demonstrates an increase in urine output accompanied by an increase in intraureteral pressure and an increase in frequency of ureteral contractions with a slight decrease in amplitude. All of the subjects receiving large intramuscular doses of adrenalin exhibited a decrease in urine output accompanied by a decrease in ureteral activity as depicted in figure 10. The effects of the adrenalin injections usually did not become apparent until 15–25 minutes after administration.

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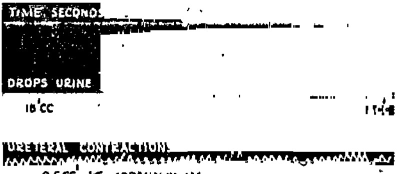
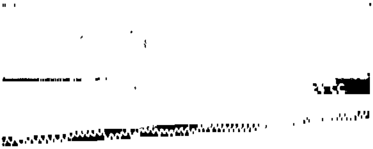
[30] Winton, F. R.: J. Physiol., 73: 151, 1931.
[31] Lucas, D. R.: Am. J. Physiol., 22: 245, 1908.
[32] Elliott, T. R.: J. Physiol., 35: 367, 1907.

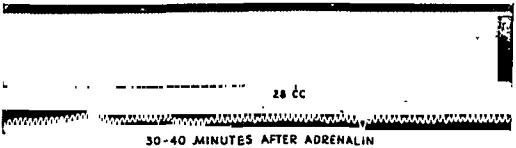
It is evident that epinephrine, simulating the effects of stimulation of the sympathetic nerves, produced no constant effect upon ureteral peristalsis. Changes in contractile activity of the ureter were obtained only when urine output was affected thus suggesting that the sympathetic nerves do not influence ureteral peristalsis by direct action upon the ureteral muscle.



0.5 cc 1/1000 ADRENALIN IM



10-20 MINUTES AFTER ADRENALIN



30-40 MINUTES AFTER ADRENALIN

Fig. 9

The effects of parasympathomimetic drugs upon ureteral contractions. Two drugs were utilized in this series of experiments, namely carbaminoylcholine and prostigmin. Carbaminoylcholine or Doryl is a synthetic derivative of choline and is the most potent of the known derivatives. It acts directly upon effector cells to produce responses which simulate those obtained from stimulation of cholinergic nerves.

Five patients were given subcutaneous doses of 0.25 mg. of Doryl with no appreciable change in ureteral activity or urine output. Figure 11 illustrates the effect of Doryl.

Prostigmine is a synthetic alkaloid belonging to the physostigmine group of drugs. It produces its effects by inhibiting cholinesterase which hydrolizes and inactivates acetylcholine. The drug has been used clinically[33, 34] to aid in the expulsion of ureteral calculi. These workers[33, 34] state that prostigmine increases ureteral peristalsis by its effect on ureteral muscle.

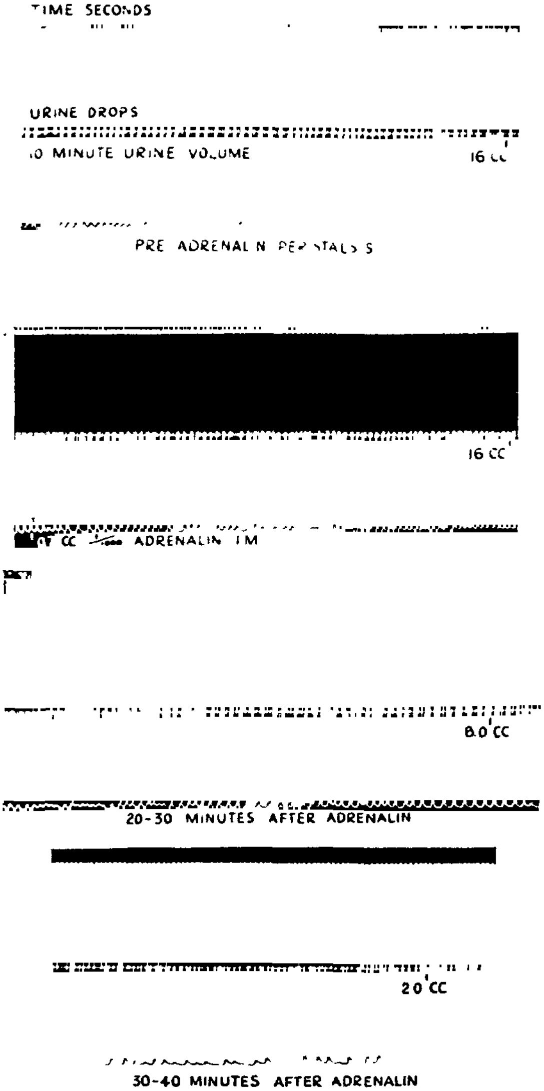


FIG. 10

Doses varying from 0.5–1.0 mg. of prostigmine methylsulfate were administered intramuscularly to 8 patients. Fifty per cent of the patients exhibited no essential change in urine output or ureteral peristalsis (fig. 12). However, in the remaining half of the patients, prostigmine affected moderate to marked

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[33] Scholl, A. J.: West. J. Surg., 48: 493, 1940.
[34] O'Conor, V. J.: Brit. J. Urol., 11: 325, 1939.

increases in urine output accompanied by appropriate changes in ureteral activity. The diuretic effect of prostigmine has been observed by Bachman[35] who used the drug in several patients with massive edema. In figure 13 it can be observed that the urine volume output increased from 4 cc/10 min/kidney to 50 cc/10 min/kidney in approximately 40 minutes; this diuresis was accompanied by an increase in intraureteral pressure and an increase in frequency and amplitude of *peristaltic contractions*.

It is thus observed that the parasympathomimetic drugs have no direct effect upon ureteral contractions by stimulation of the cholinergic nerves; any observable change in peristalsis was due to the increase in urine output produced by prostigmine administration.

Summary. Stimulation of the sympathetic effector cells by epinephrine and of the parasympathetic system by carbaminoylcholine and prostigmine, effected no change in ureteral peristalsis by *direct action on the ureteral muscle*. Variances in ureteral peristalsis were observed *only* when there were changes in urine excretion—an increase in urine output producing increased ureteral activity while a diminution in urinary excretion resulted in decreased ureteral contractility. The activity of ureteral muscle is apparently not affected by the autonomic nervous system.

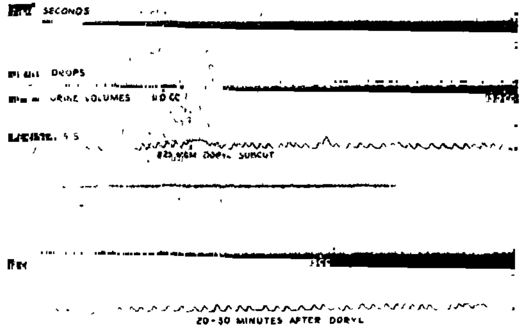

FIG. 11

OBSERVATIONS ON THE EFFECTS OF DRUGS REPUTED TO HAVE SMOOTH MUSCLE RELAXING OR STIMULATING QUALITIES, ON URETERAL CONTRACTILITY

Effect of the nitrites upon ureteral tone and peristalsis. It has been stated that the nitrites relax the excised ureter and that a similar antispasmodic action on the intact ureter is manifested clinically[36]. The nitrite ion acts directly upon smooth muscle to produce its antispasmodic effect.

Wchnschr., 21: 935, 1940.

The Pharmacological Basis of Therapeutics, New York:

Th. :

Five patients were used in this series of experiments. Each patient was given 1.2 mg. of nitroglycerin sublingually and some were given amyl nitrite 30 minutes later. Peristalsis and tonicity were not decreased in any of the experiments. In figure 14 it will be seen that nitroglycerine did not depress ureteral activity but appeared to increase it; the increase was due to abdominal straining.

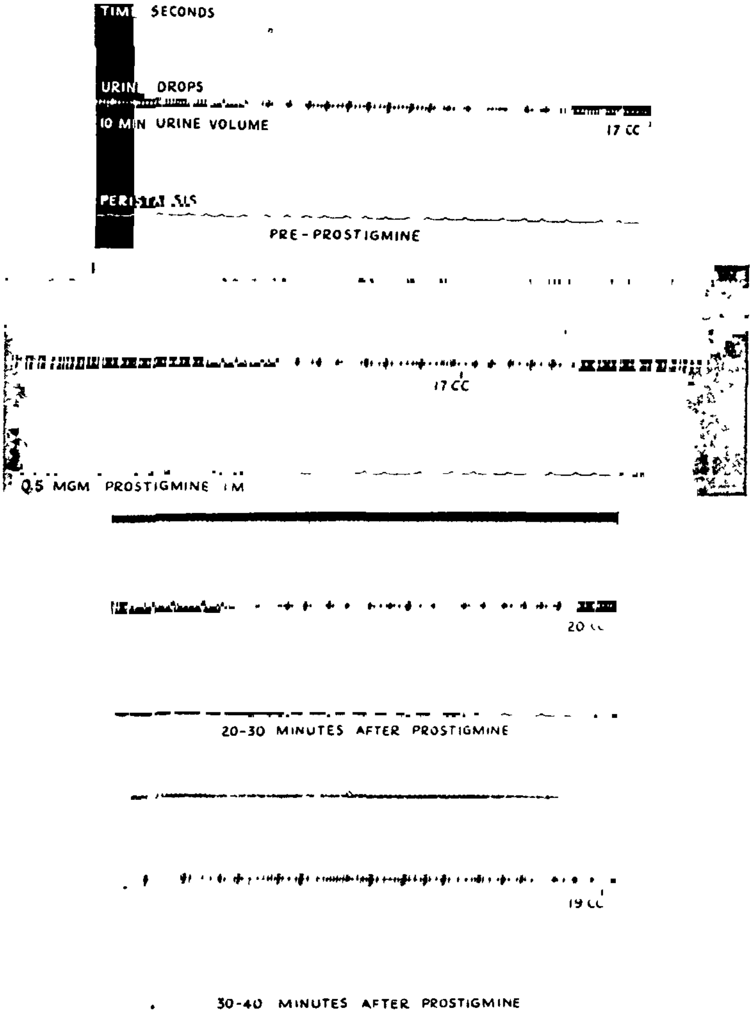

FIG. 12

Effects of the opium alkaloids on ureteral activity. Three alkaloids of opium will be considered namely morphine, papaverine and its ethyl analogue, perparine. Morphine is the most important member of the phenanthrene group while papaverine is the main alkaloid of the benzylisoquinoline group.

Effect of morphine on ureteral peristalsis. It has been demonstrated by Macht[37] and Gruber[38] that morphine will produce an increase in the contractions and tonicity of the *excised ureter.* Ockerblad, Carlson and Simon[25] observed that morphine, given subcutaneously in doses of 0.008–0.32 gm., produced a marked increase in ureteral tone and in the amplitude of peristaltic contractions in *24 patients.* They noted that the morphine effect became apparent 2 to 5 minutes after injection and that it persisted for 3 or more hours. It will be noted that all of the 24 patients reacted in the same manner toward morphine administration. Trattner, whose discussion of the subject is included in the article, stated that he had performed morphine experiments on 9 patients and had obtained 3 types of results. In 5 patients he had observed an increase in the amplitude of the peristaltic waves; the increase was fleeting in one but prolonged in the others.

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[37] Macht, D. I.: J. Pharmacol. and Exper. Therap., 9: 197, 1916.

[38] Gruber, C. M.: J. Pharmacol. and Exper. Therap., 33: 191, 1928.

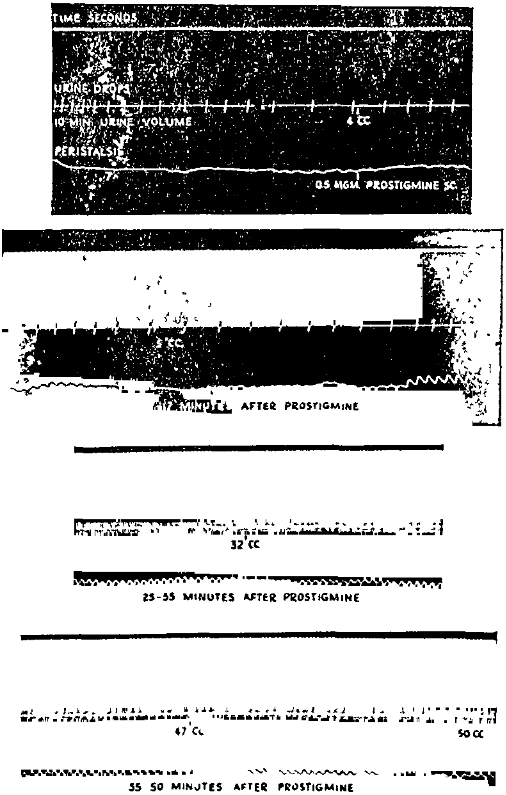

FIG. 13

He noted that in 2 other patients no effect was exhibited and this, he stated, was due to the fact that the ureters were the seat of inflammatory infiltration. In the 2 remaining subjects it was observed that morphine had a quieting effect on ureteral activity; no explanation was offered for this phenomenon.

In analyzing Trattner's observations it is quite apparent that one-half of the subjects either showed no effect or a decrease in ureteral activity. This does not correlate well with Ockerblad's work in which 100 per cent of the patients demonstrated an increase in intraureteral tone and in amplitude of peristaltic contraction. Further analysis of both investigators' experimental methods indicates that apparently no effort was made to check on the changes in urine output that might have occurred during each experimental observation. Failure to check on the urine excretion will result in fallacious observations and conclusions since it has been demonstrated by numerous investigators, including the present writer, that the normal adequate stimulus for ureteral peristalsis is the production of urine by the kidneys. It is believed that the stimulation is effected through stretching of the ureteral muscle by the urine. It has also been shown that as urine volume per unit time is increased, there is an increase in ureteral activity. Conversely if urine output decreases, there is a resultant decrease in ureteral motility. Thus it is entirely possible that the various observations made on the effect of morphine on the intact human ureter, were nothing more than the reactions of the ureter to changing urine outputs rather than the reactions of the ureteral muscle per se to morphine. Haines[25] made this observation in his discussion of Ockerblad's work.

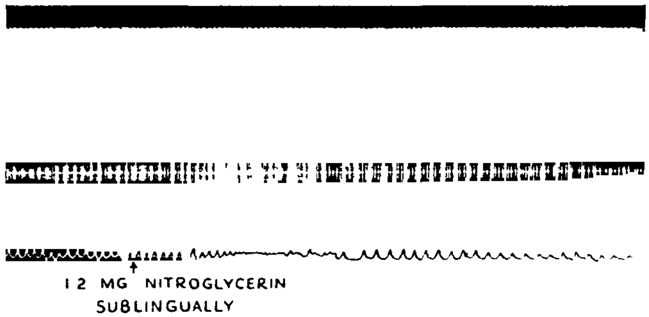

FIG. 14

Observations were conducted on 10 patients. Fluids were not forced on these patients since it was desired to simulate Ockerblad's experimental procedure as much as possible. Five patients were given doses of 0.016 gm. of morphine subcutaneously and 5 were given doses of 0.010 gm. of morphine intravenously. Urine outputs were checked as usual by measuring 10 minute volumes obtained from the pelvis of the opposite kidney. Incidentally it has been demonstrated by Klisiecki et al.[39] that normally both kidneys put out approximately the same amount of urine over a short period of time; this has been verified by the writer.

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[39] Klisiecki, A., Pickford, M., Rothschild, P. and Verney, E. B.: Proc. Roy. Soc. London, s.B. **112:** 496, 1933.

Three types of ureteral response to morphine, irrespective of route of administration, were observed. Two patients demonstrated no change in ureteral peristalsis, 3 patients exhibited an increase in ureteral activity and 5 patients

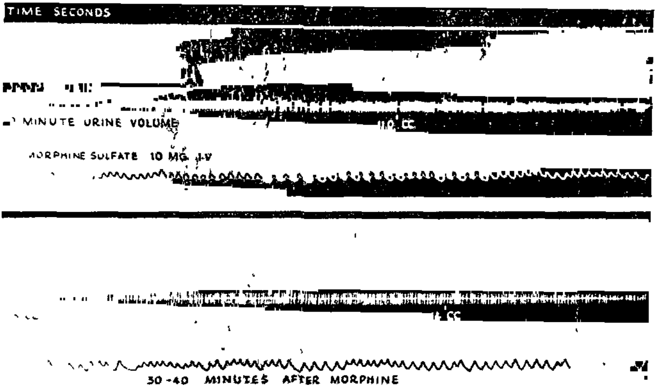

Fig. 15

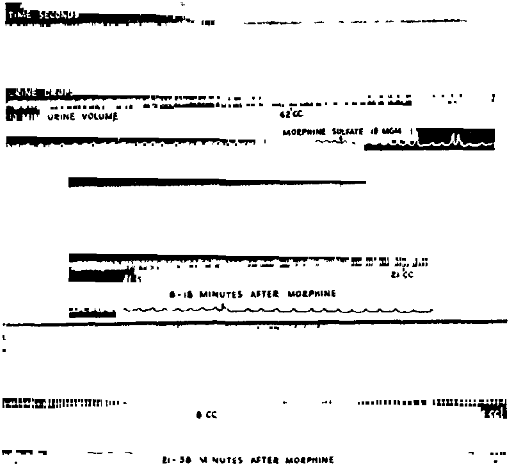

Fig. 16

demonstrated a decrease in ureteral contractility. Figure 15 illustrates no essential change in peristalsis or intraureteral pressure following administration of morphine; it will be observed that urine output has remained approximately constant. In figure 16 it can be seen that there is a gradual diminution in ureteral peristalsis following the intravenous injection of 0.010 gm. of morphine sulfate. It will also be observed that urine output gradually diminished from 42 cc/10 min/kidney to 5 cc/10 min and that the decrease in ureteral peristalsis coincided with the drop in urine output. An increase in ureteral contraction and intraureteral pressure can be observed in figure 17. This again coincided with an increase in urine output from 0 cc/10 min to 7 cc/10 min.

On the basis of these observations it is postulated that (1) morphine, in the doses used, has no direct effect upon ureteral tone and peristalsis and (2) that morphine can be used without atropine and without fear that it will produce increased spasm of the ureter in cases of renal or ureteral colic.

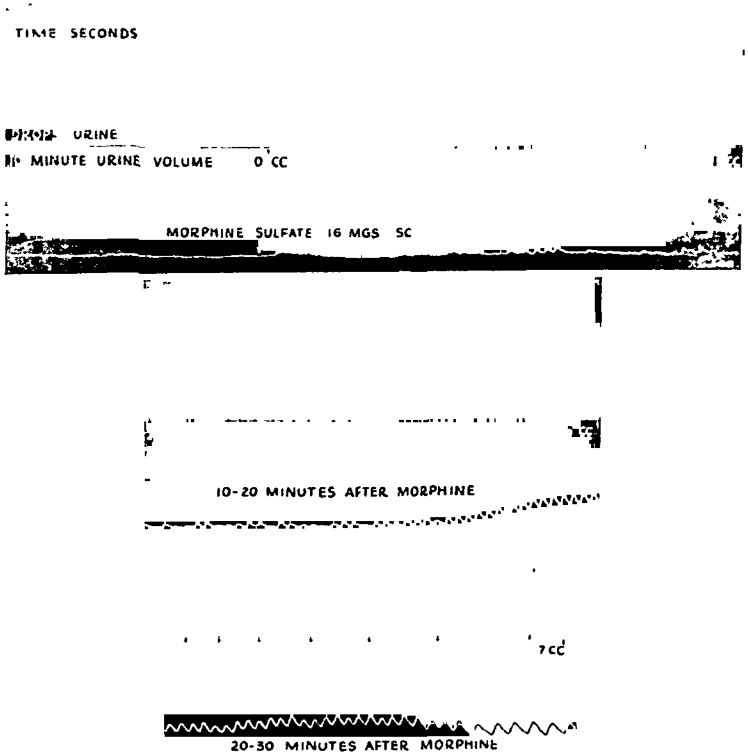

FIG. 17

Effect of papaverine and perparin on ureteral peristalsis. Macht[37] and Gruber[38] observed in their experiments that papaverine produces a slowing or total inhibition of contractions and decreased tonus in the excised ureter. Macht and Geraghty[40] introduced papaverine intraureterally and observed that it caused a dilatation of the ureteral orifice; they stated that it facilitated the passage of calculi. In experiments on the intact human ureter Trattner[26] noted that papaverine had a questionable effect on the ureter.

Observations were carried out on 15 patients, 10 of whom were given intravenous doses of 100–120 milligrams of papaverine hydrochloride (2 per cent solution) and 5 of whom were given intraureteral injections of 3–5 cc of a 2 per cent solution of papaverine hydrochloride. *No effect on ureteral peristalsis or intraureteral pressure was noted in any of the experiments in which the urine volume output was constant.* Figure 18, *A* and *B* illustrates the effect of intravenous administration of 125 milligrams of papaverine hydrochloride. The effect of

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[40] Macht, D. I. and Geraghty, J. T.: Bull. Johns Hopkins Hosp., 27: 119, 1916.

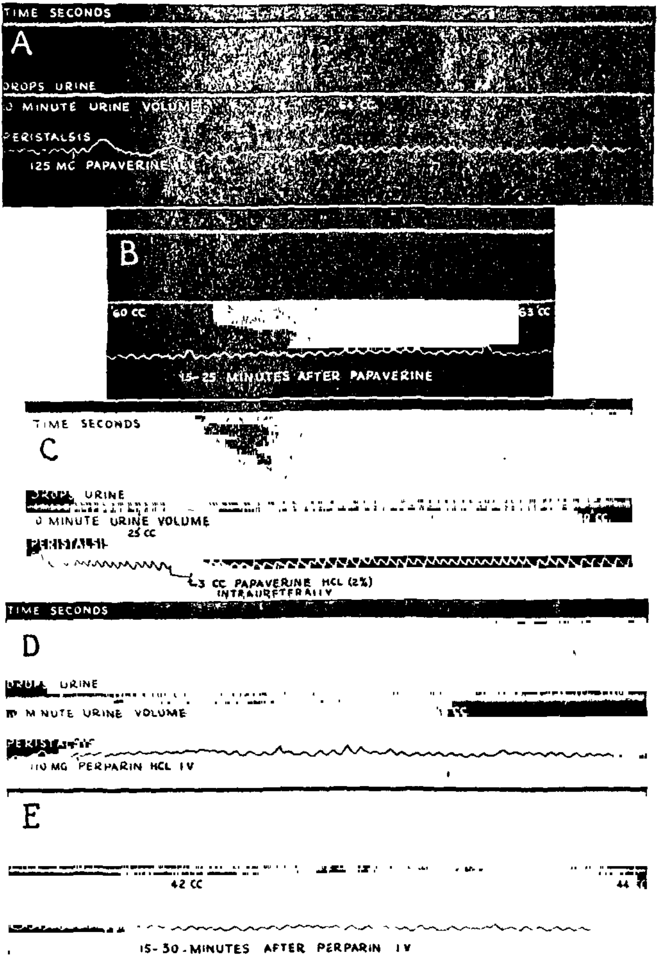

FIG. 18

intraureteral injection of 3 cc of a 2 per cent solution of papaverine hydrochloride is illustrated in figure 18, *C*.

Intravenous injection of 110 milligrams of perparin hydrochloride in 2 patients elicited no changes in ureteral activity (fig. 18, *D* and *E*).

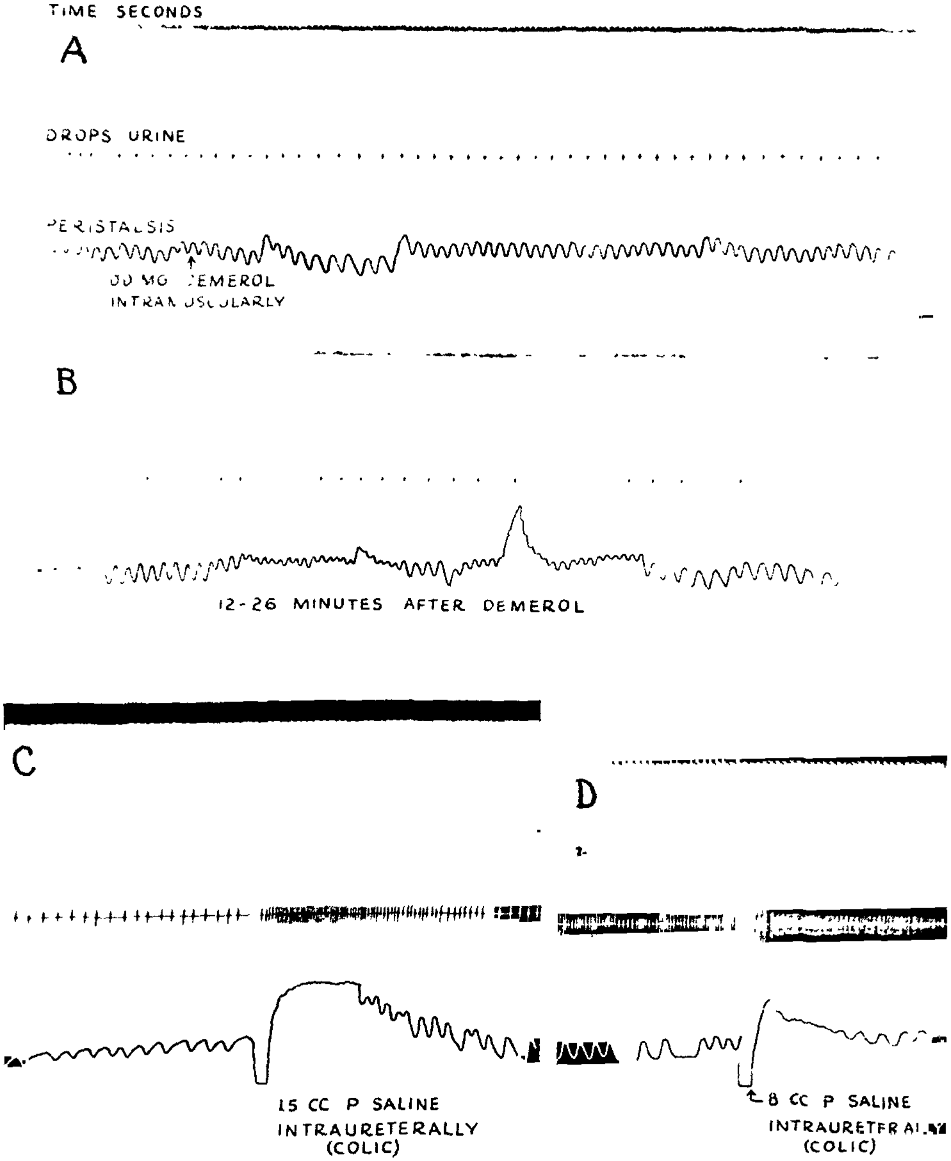

FIG. 19

It is rather difficult to visualize the efficacy of intraureteral injections of drugs for the purpose of therapeusis in colic. It has been commonly observed that intraureteral injection of fluid will result in increased intraureteral pressure and peristalsis with a resultant rapid expulsion of the injected fluid. This expulsion will begin to take place as soon as the syringe is removed from the catheter and will have been all expelled within several minutes. In addition, if the kidney is excreting 4–6 cc of urine per minute, one can readily see the rapidity with which the injected solution would be evacuated Plugging the end of the catheter has been utilized in an attempt to keep the solution in the pelvis and ureter This procedure has been used in our experiments on intraureteral injection of various substances but no differences were noted

The effect of Demerol upon ureteral contractility Demerol, the ethyl ester of 1-methyl-4 phenylpiperidine-4 carboxylic acid, is stated to be a powerful spasmolytic agent Climenko and Berg[41] observed that the intramuscular injection of 75 milligrams of Demerol produced a diminution in tonus of the ureter associated with a marked decrease in amplitude of contractions in fourteen patients However, Gruber, Hart and Gruber[42] concluded from their experiments on dogs that Demerol shows no promise of value as a spasmolytic agent on intact smooth muscle *They also noted that the effects of the drug on urine secretion are uncertain: if there is an action, it is that of decreased secretion*

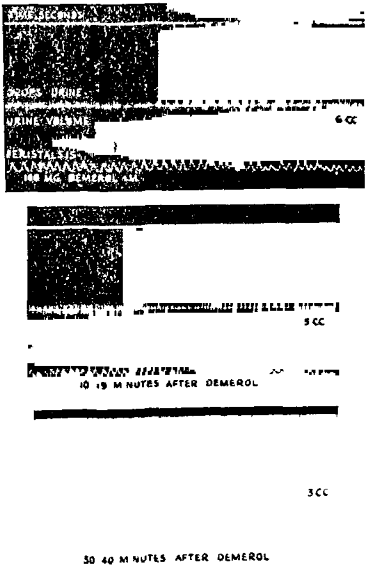

Fig 20

Experimental observations were conducted on 10 patients each of whom were given 100 milligrams of Demerol intramuscularly It was noted in all of the experiments that Demerol produced a definite decrease in urine secretion. This decrease in secretion was accompanied by a diminution in ureteral activity in all of the subjects except one. This patient, after ureteral catheterization, developed colic which persisted throughout the experiment despite the injection of 100 mg. of Demerol intramuscularly. The record (fig. 19, *A* and *B*) of her ureteral activity demonstrated contractions which were not related to urine output and which showed no change after administration of Demerol. It is believed that her colic was due to these contractions. Several of these patients, while under the influence of Demerol, exhibited symptoms of pain to the rapid intraureteral injection of physiological saline. Figure 19, *C* and *D* illustrates the reactions of 2 of the patients to the rapid injection of saline intraureterally despite previous Demerol medication.

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[41] Climenko, D R and Berg, H J Urol 49 255, 1943

[42] Gruber, C M, Hart, R L and Gruber, C M Jr, J Pharmacol and Exper Therap, 73 319, 1941

The typical response to Demerol is observed in figure 20. It will be observed that there is a gradual decrease in urine output accompanied by a decrease in amplitude of contractions and intraureteral pressure.

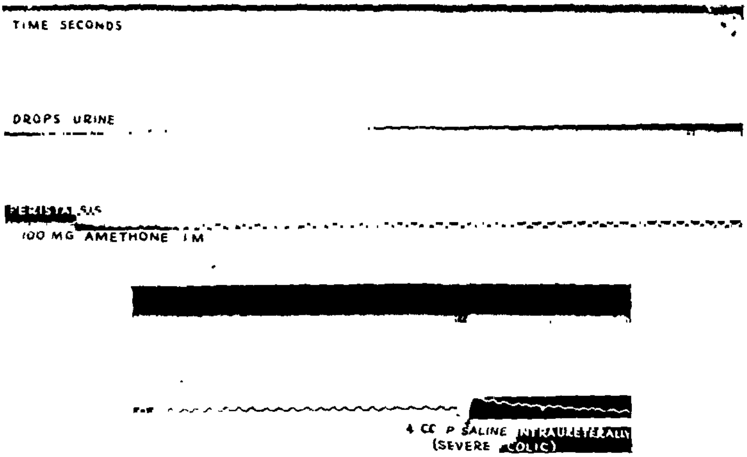

FIG. 21

On the basis of these observations it is postulated that Demerol does not have a spasmolytic action on ureteral muscle. The decreased peristaltic activity observed after Demerol administration is due to the diminution in urine secretion effected by the drug.

The effect of Amethone on ureteral peristalsis. Prince and Richardson[43] have observed that Amethone, a benzofuranone derivative, relieved pain caused by spasm of the smooth muscle of the urinary tract. It has been found that Amethone inhibits the contractions of the isolated ureter of the dog.

Tracings of ureteral activity were obtained on 5 patients each of whom were given 100 milligrams of Amethone intramuscularly. No effects on peristalsis or intraureteral tone were noted. Amethone did not prevent the production of pain by intraureteral injections of physiological saline. Figure 21 demonstrates the typical response of the ureter to Amethone.

The effect of Depropanex on ureteral peristalsis. It is believed by Carroll and

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[43] Prince, C. L. and Richardson, E. J., Jr.: J. Urol., 54: 75, 1945.

Zingale[58] and Lazarus[59] that pancreatic tissue extract exerts an antispasmodic effect upon the ureter. They[58] have found that the preparation will cause a complete cessation of the ureteral wave within a minute and a half after its administration.

Experimental observations were conducted on 5 patients. Each patient was given 6 cc of Depropanex intramuscularly. It will be noted that 6 cc is twice the dose utilized by Carroll in his observations. It was found that Depropanex did not have the slightest effect on ureteral activity in any of the subjects tested (fig. 22, *A* and *B*).

The effect of calcium levulinate on ureteral activity. Bauer, Salter and Aub[44] noted that the slow intravenous administration of 20 cc of a sterile solution of 5 per cent calcium chloride promptly relieves the severe pain of colic caused by ureteral stone. Trattner[76] observed that calcium gluconate decreased ureteral peristalsis in some cases and in some cases had no effect.

No diminution in ureteral activity was observed after the intravenous injection of 15–20 cc of a 10 per cent solution of calcium levulinate in 5 patients. The administration of calcium did not prevent the appearance of pain produced by the intraureteral injection of physiological saline. In figure 22, *C* it can be observed that no change in peristalsis occurs after intravenous administration of calcium. It will also be noted that the ureter responded normally to the intraureteral injection of saline.

The effect of intraureteral injection of Avertin upon ureteral activity. It has been observed by Waddell[45] that the introduction of tribromethanol (Avertin) into the intact ureter will depress ureteral peristalsis, tone and increase the patency of the ureter. Jarman and Scott[46] found that the intraureteral injection of Avertin hastened the passage of ureteral calculi.

Five patients were used in this series of experiments. A normal tracing of ureteral activity was first obtained. Then 6–10 cc of a 2½ per cent solution of Avertin with Amylene Hydrate was slowly injected into the ureter and the caudal end of the ureteral catheter plugged. After 10 minutes the catheter was unplugged and connected to the ureterometer, a tracing was then obtained. It was observed that Avertin had no effect upon ureteral peristalsis or tone. Figure 22, *D* demonstrates the lack of relaxation or depression of peristalsis following intraureteral injection of tribromethanol.

The effect of Lipo Lutin on ureteral activity. Traut and McLane[47] observed that the ureters in women dilate during pregnancy. They believe that the dilatation is dependent on some unexplained chemical basis. Hundley, Diehl and Diggs[48] administered progestonic substances to non-pregnant women over a period of several months and noted that a decrease in ureteral peristalsis was produced.

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[44] Bauer, W., Salter, W. T. and Aub, J. C.: J.A.M.A., 96: 1216, 1931.

[45] Waddell, J. A.: J. Urol., 29: 707, 1933.

[46] Jarman, D. W. and Scott, W. W.: J. Urol., 38: 111, 1937.

[47] Traut, F. H. and McLane, C. M.: Surg., Gynec. & Obst., 62: 65, 1936.

[48] Hundley, J. M. Jr., Diehl, W. K. and Diggs, E. S.: Am. J. Obst. and Gynec., 44: 858, 1942.

On the basis of the above findings it was decided to use enormous doses of Lipo-Lutin (a corpus luteum extract containing 2 international units of progesterone per cc.) in an attempt to depress ureteral activity within 2 hours after administration. Four patients were given 10–20 cc of Lipo-Lutin intramuscularly. In order to facilitate absorption one-fourth of the total dose was injected into 4 different areas. *It was observed that ureteral activity was not depressed in any of the experiments.* Figure 23 illustrates the effect of intramuscular injection of 20 cc of Lipo-Lutin on ureteral peristalsis.

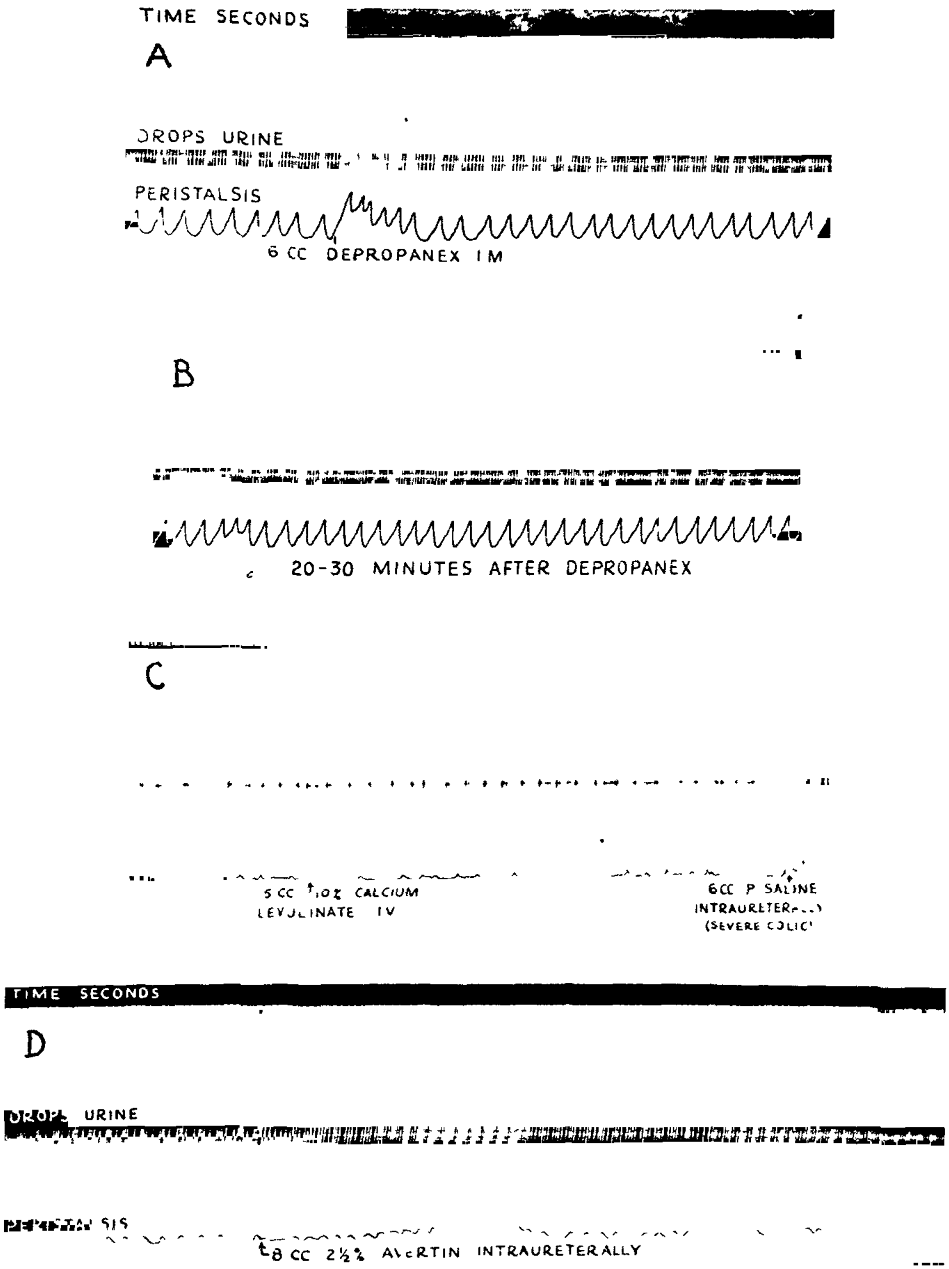

Fig. 22

The effect of Pitressin on ureteral peristalsis. Pitressin is a posterior pituitary preparation which contains 10 units of pressor activity and less than one-half unit of oxytocic activity per cc.[35] This preparation exhibits a predominant vasopressor—anti-diuretic activity. Pitressin demonstrates several actions when it is administered to man. It will produce a marked constriction of the capillaries[49] increased intestinal peristalsis[50] and an inhibition of water diuresis[51, 52, 53, 54]. It has been postulated that Pitressin produces increased tonicity and spasm of the ureter by direct action upon the smooth muscle cells.

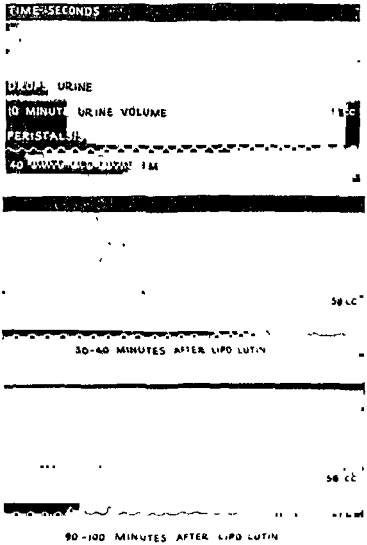

Fig. 23

To determine the effects of Pitressin upon ureteral activity observations were made on 5 patients. Fluids were forced in 3 patients in order to insure water diuresis during the experiments. These patients were each given an intramuscular injection of 20 units of Pitressin. All 3 patients demonstrated a marked decrease in urine output accompanied by a decrease in ureteral activity. It will be observed in figure 24, *A* and *B* that urine volume is decreased from 27 cc/10 min/kidney to 19 cc/10 min following administration of pitressin. A marked decrease in intraureteral pressure accompanied the diminution in urine output.

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[49] Oliver, G. and Schafer, E. A.. J. Physiol., **18:** 277, 1895.
[50] Guthrie, J. S. and Bargen, J. A.: Surg., Gynec. & Obst., **63:** 743, 1936.
[51] Ross, J. B. and Stehle, R. L.: J. Pharmacol. and Exper. Therap., **38:** 451, 1930.
[52] MacDonald, A. D.: Quart. J. Exper. Physiol , **23:** 319, 1933.
[53] Priestley, J. G.· J. Physiol., **55:** 305, 1921.
[54] Theobald, G. W.: Clin. Sc., **1:** 225, 1934.

Fluids were not forced in the remaining 2 patients in order to observe the effect of Pitressin in subjects who did not demonstrate a water diuresis. Both of these patients exhibited no change in urine output or ureteral peristalsis following injection of 20 units of Pitressin (fig. 24, *C* and *D*).

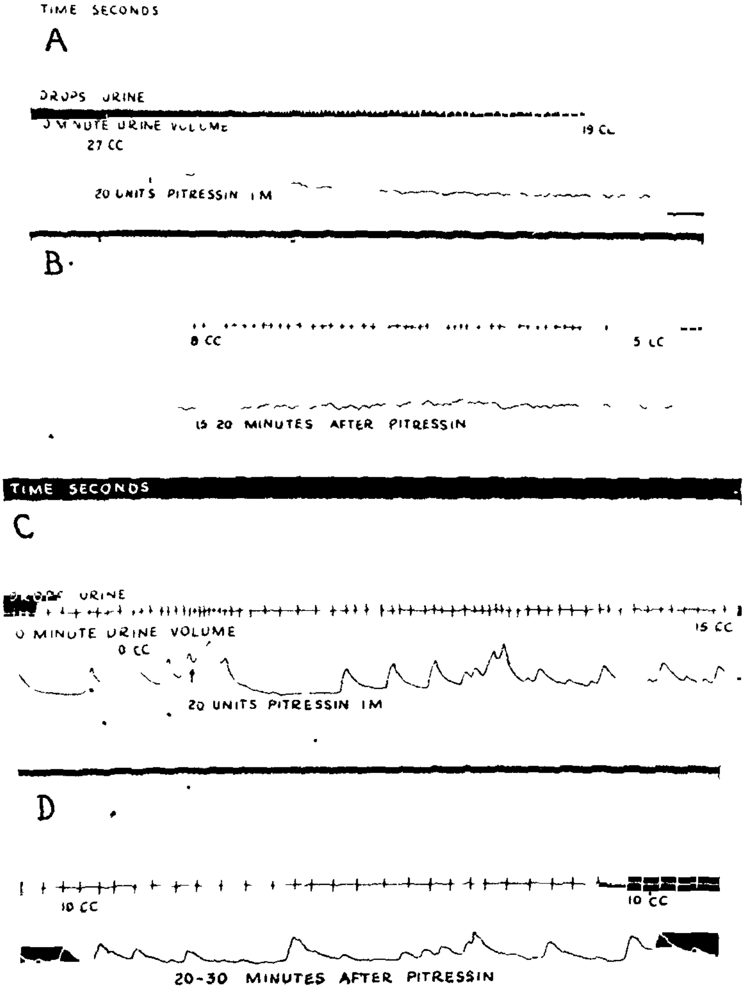

Fig. 24

The results in this series of experiments clearly illustrate the fact that Pitressin does not increase tonicity of the ureter. With water diuresis Pitressin will effect a decrease in urine output with a resultant diminution in ureteral contractility. But, if water diuresis is absent, Pitressin will not affect urine output and there will be no change in ureteral tone or peristalsis.

The effect of Benadryl upon ureteral activity. Benadryl, beta-dimethyl-amino-ethyl-benzhydryl ether hydrochloride, is a synthetic preparation with marked antihistamine properties. It is thought to act by competing with histamine for a given site of action or receptive substance. Benadryl is 650 times as effective as papaverine in antagonizing histamine and 50 times as effective as papaverine in antagonizing acetylcholine.

In figure 25 *A* and *B* it can be observed that an intravenous injection of 50 mg of Benadryl had no effect on normal ureteral activity.

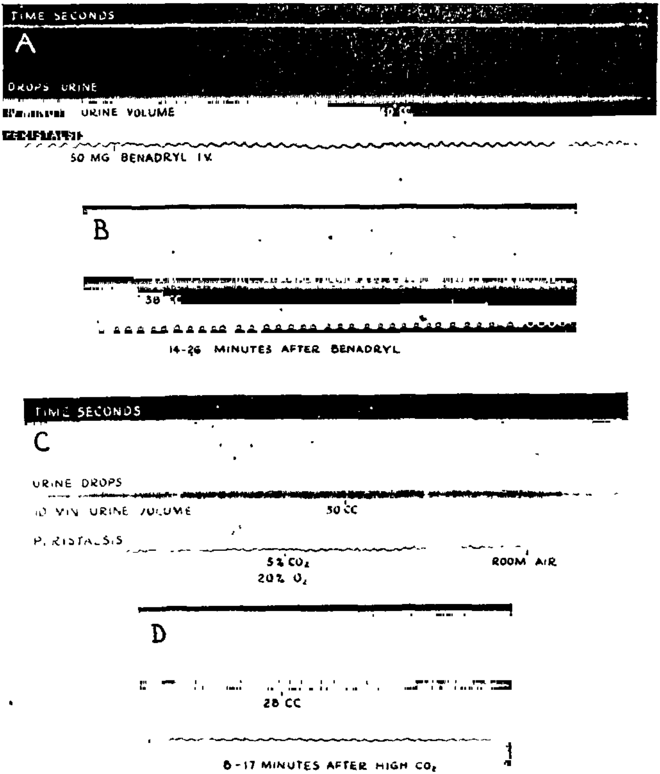

FIG. 25

The effect of Hypercapnia and Anoxia on ureteral activity. It has been demonstrated[55] that an increase on H-ion concentration caused a relaxation of the tonus of smooth muscle. If plain muscle is deprived of oxygen, tonus cannot be sustained. With the above two facts in mind it was decided to investigate the effect of rebreathing a mixture of 20 per cent oxygen and 5 per cent CO_2 on ureteral activity. Figure 25, *C* and *D* illustrates the effect of low O_2—high CO_2 upon ureteral tonus and peristalsis. The patient rebreathed the original mixture of oxygen and CO_2 for a period of 6 minutes at the end of which time the patient demonstrated marked hyperpnea and cyanosis. No demonstrable effect on ureteral activity was noted.

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[55] Evans, C. L.: Physiol. Rev., 6: 358, 1926.

It is believed that the lack of response of the ureter to the above procedure was due to the fact that the rebreathing was not conducted for a period sufficiently long enough to affect the cellular metabolism. It is well known that smooth muscle uses oxygen at a very slow rate.[55]

SUMMARY

It has been attempted, in this experimental study, to correlate the many controversial observations made on the physiology of the ureter and, to evolve a simple, logical picture of the process of peristalsis in the normal intact human ureter. In vitro studies on excised isolated ureters will not be considered since it is believed that experimental conditions in these procedures are highly unphysiological and, in many instances, the findings are not applicable to the intact human structure.

Many of the studies on the intact human ureter have been inadequately controlled and consequently the conclusions drawn from these experiments are open to criticism. There has been an almost universal failure on the part of investigators to check the volume of urine excretion during their experimental runs. It has been adequately demonstrated by numerous investigators, including the author, that changes in urine volume output will produce, within certain limits, an increase or decrease in ureteral activity. Thus it can be readily seen that one cannot judge the action of a drug on the ureter if the intensity of the normal stimulus for ureteral peristalsis is unknown. A good illustration of the point in question is the action of Pitressin. Pitressin will definitely decrease urine output if water diuresis is present. Thus, if an investigator were to record ureteral peristalsis in a well hydrated patient who had received Pitressin, he would note a decrease in ureteral activity. If urine excretion were not followed, he could readily postulate that Pitressin exerts a spasmolytic action upon the ureter. However, a check on urine volume output would soon demonstrate that the urine excretion was reduced. The next step in the procedure would involve administration of Pitressin to a patient not exhibiting a water diuresis. The investigator would then observe that urine output and ureteral activity were not affected. He would then correctly conclude that Pitressin had no direct effect upon the smooth muscle of the ureter.

Studies on the effect of mechanical stimuli upon ureteral contractility have demonstrated that mechanical stretching of the ureteral muscle will initiate and vary peristaltic activity. In the normal individual intraureteral pressure or distension of the lumen is altered by the volume of urine excretion from the kidney, peripheral resistance or intravesical pressure and intra-abdominal pressure. It has been demonstrated that an increase of any one of the factors, provided the other two remain approximately constant, will result in increased ureteral activity Thus, if intra abdominal and intravesical pressures are constant, an increase in urine excretion will result in an increase in ureteral peristalsis, within limits The qualifying phrase "within limits" has been used several times in discussing the relationship of peristalsis to urine excretion and it would be well to clarify this phrase now Ureteral peristalsis does not bear a constant straight line relationship to urine output, i e , increasing urine volume excretions are not accompanied by proportionate increases in amplitude, and frequency of ureteral contractions It has been frequently observed that a large urine volume excretion may be accompanied by a high intra-ureteral pressure and no visible peristaltic waves Increased ureteral activity may manifest itself in many forms namely (a) an increase in amplitude with no change in frequency of peristaltic waves (b) an increase in frequency but no change in amplitude (c) an increase in frequency and amplitude (d) an increase in frequency with a decrease in amplitude (e) an increase in amplitude with a decrease in frequency and (f) a decrease in both amplitude and frequency of peristaltic contractions with an increase in intra-ureteral pressure The intra-ureteral pressure or ureteral tone has been found to bear a more mathematical straight line relationship to urine output than peristaltic contractions It has also been observed that a change in urine output, when the excretion is small, will effect a much greater change in peristalsis than when the urine volume output is great, e g , an increase from 2 cc/10 min/kidney of urine excretion to 10 cc/10 min may result in a marked increase in amplitude and frequency of ureteral peristalsis while an increase from 50 cc to 65 cc of urine/10 min/kidney may barely cause a perceptible change in peristalsis

In the past many investigators have lamented the fact that an adequate drug for blockade of the autonomic system was not available as curare was for skeletal muscle Recently however, tetraethylammonium, a quaternary ammonium salt, has become available for research purposes It acts on both the sympathetic and parasympathetic ganglia to produce a blockade to transmission of nerve impulses across these ganglia Utilizing this drug it has been found that ureteral peristalsis will continue despite chemical interruption of the sympathetic and parasympathetic nerve impulses This observation was substantiated by experiments in which high spinal anesthesia and atropine were utilized This confirmed the postulation that ureteral peristalsis will continue despite interference with the nerve supply to the ureters Further studies were conducted with curare in order to rule out the very remote possibility that somatic nerves may play a part in ureteral peristalsis It was found that curare did not affect ureteral peristalsis

Having ascertained that the autonomic nervous system (including any ganglia present in or around the ureter) was not essential for the maintenance of ureteral peristalsis, it was then necessary to determine whether stimulation of the sympathetic (adrenergic) or parasympathetic (cholinergic) effector mechanism could influence ureteral peristalsis *The use of epinephrine, Prostigmine and carbaminoylcholine effected no change in ureteral peristalsis by action upon the* *smooth muscle of the ureter through the autonomic nervous system.* Epinephrine affected ureteral activity indirectly by modifying its normal stimulus, namely urine secretion. Small doses of epinephrine either produced no change or an increase in urine output which was accompanied by no change or an increase in ureteral activity. Large doses of epinephrine always produced a decrease in urine excretion accompanied by a decrease in ureteral activity. Doryl, a powerful parasympathomimetic drug, did not change urine output or ureteral peristalsis. Prostigmine increased urine output in 50 per cent of the patients tested with the drug; the increased urine output was accompanied by increased ureteral activity. The remaining 50 per cent of the patients showed no change in urine output or ureteral peristalsis.

Because of the fact that ureteral peristalsis and ureteral tone are not affected by blockade or by stimulation of the sympathetic and parasympathetic nervous systems, it is believed that the ureter is an autonomous organ. The peristaltic contractions of the ureter do not originate from impulses sent from the central nervous system. The autonomic ganglia take no part in maintaining ureteral contractility. It is probable that the nerve supply of the ureter contains only vasomotor and sensory fibers.

Correlating and integrating the material presented thus far in the discussion, it is apparent that normal ureteral peristalsis is a simple process. The normal intact human ureter is comparatively quiescent when no urine is being excreted by the kidneys. As soon as urine flows into the calyces, peristaltic contractions are initiated[56] which are transmitted down through the ureter purely on a myogenic basis. If the urine output is increased sufficiently, there will be an increase in ureteral peristalsis. A decrease in urine output will be accompanied by a decrease in ureteral contractility. In the normal individual intra-abdominal and intravesical pressure are approximately constant. It has been shown[19, 57] that the intravesical pressure remains constant with increasing volumes of urine until the detrusor actually contracts. Thus the only variable will be urine output, and it is this factor which is the normal adequate stimulus for rhythmic contractions of the ureter. It is not the composition of the urine which stimulates peristalsis primarily, but the volume of urine by the mechanical process of stretching the ureteral muscle fibers. Ureteral peristalsis is entirely independent of the central nervous system.

Parenteral administration of therapeutic doses of Amethone, Depropanex, calcium levulinate, Demerol, Lipo-Lutin, morphine, papaverine, Perparin, nitroglycerine, amyl nitrite, Benadryl, Trasentin, atropine and Pitressin demonstrated no direct effect upon ureteral tone and peristalsis. Ureteral activity was not varied by the intraureteral injection of either papaverine or Avertin. Any change in ureteral peristalsis occurring after the administration of one of the above mentioned drugs can be directly attributed to a change in urine output.

[56] Narath, P. A.: J. Urol., **43:** 145, 1940.
[57] Mosso, A. and Pellacani, P.: Arch. ital. de biol., **1:** 97, 1882.
[58] Carroll, G. and Zingale, F. G.: South. Med. J., **31:** 233, 1938.
[59] Lazarus, J. A.: J. Urol., **43:** 102, 1940.

If the urine volume is kept constant, no change will be observed in ureteral tone or peristalsis Demerol, Pitressin and large doses of epinephrine will produce a decrease in urine excretion *It would be well to emphasize the fact that morphine does not produce increased tonus or peristalsis of the ureter as has been postulated* Observations made in this experimental study clearly demonstrate the absence of any direct stimulating effect of morphine on ureteral activity, this fact is substantiated by a re evaluation of Trattner's data *Since morphine has no effect* upon the ureter, it is apparent that it can be administered alone in cases of renal or ureteral colic without fear of causing increased spasm of the ureter

No drug (*in the therapeutic dose*) used in this study produced a decrease in tonus or peristalsis of the normal ureter Apparently mechanical stretching of the ureteral muscle by the use of inlying catheters is still the only satisfactory therapeutic method of producing dilatation and decreased tonus of the ureter

It can be emphasized again that the ureter is a highly specialized involuntary organ which is probably autonomous

CONCLUSIONS

It is postulated that tonus and rhythmic contraction of the intact human ureter are entirely independent of the central nervous system including the autonomic nervous system and all its ganglia

The normal adequate stimulus for the initiation and maintenance of ureteral peristalsis is a stretching of the smooth muscle fibers of the ureter by the urine excreted from the kidney

Peristaltic activity of the ureter can be altered by changes in urine volume output, within certain limits

Rhythmic contractions and tonus of the intact human ureter were not directly affected by administration of tetraethylammonium chloride, procaine high spinal anesthesia, Doryl, epinephrine, prostigmine, atropine, Trasentin, Amethone, Depropanex, calcium levulinate, nitroglycerine, amylnitrite, papaverine, perparin, Lipo Lutin, Pitressin, Avertin (intra ureterally), Benadryl, Demerol and morphine

Demerol, Pitressin and large doses of epinephrine produced a decrease in urine secretion

Prostigmine acted as a diuretic in one-half of the patients to whom the drug had been administered

No drug depressed ureteral peristalsis or decreased the tonus of the ureter

Morphine does not produce increased peristalsis and tonicity of the ureter

DISCUSSION

Dr. Harry R. Trattner (Cleveland, O.): I wish to express admiration for Dr. Lapides' investigations covering some fundamental aspects of the vitally important subject before us.

The author does not concur as to the value of ureteral studies in vitro due to grossly artificial conditions. Thus surprisingly and with intention he excludes the data of many observers that certain drugs have a direct influence on the ureter. My own experience in studies of excised and intact ureters has led me to believe that findings obtained in this comparative manner are more definite in evaluating many influences including that of drugs, for certain problems require due consideration, or elimination of vital processes so that single factors can be more precisely controlled. As examples may be mentioned the individual or simultaneous activity of longitudinal and circular coats of the ureter in their relation to outflow control and tambour lever movements, pH factor, etc.

The author infers that since peristalsis runs parallel to urinary output "within limits", that when certain drugs were administered which influenced this output, such effects could not be attributed to any direct action on the ureter, but instead to effects on renal circulation, either locally or operating indirectly on the renal through the general circulation. The comprehension that the urine or rate of excretion principally or preferably determines the influence on ureteral movement, and is of great importance in pharmacological considerations appears factual and in agreement with most observers. For purpose of clarity I will not include drugs or conditions in which the factor of blood pressure is obvious or significant, for there could be little disagreement as to the chief factor involved.

The intimate relationship between primary and secondary factors in cause and effect is often difficult of analysis not only because of physical or chemical action and interaction, the one being dependent on the other for continuation of the process, but also in view of possible shift of a secondary factor into the primary position. For example, such an interrelated mechanism is involved in glomerular filtration and tubular absorption.

Though the functional activity of the kidney is dependent on its blood flow and glomerular pressure, it probably also depends on its muscular -excretory passages to a much greater extent than has been assumed. Some experimental data relating to this point have been supplied by Lucas. In addition, clinical observations indicate that reduction of the motor functional capacity of the ureter alters, interrupts or injures the process of renal excretion. A cardinal question confronts us in studies of the *intact* organ, namely: What is the logic in regarding the ureter entirely separate from its renal pelvis, infundibula and calyces? The fact that the renal circulation can be altered by change of intrapelvic pressure (oncometer experiments) indicates in all probability that a mechanical effect on this circulation can be exerted by various states of the musculature of the upper urinary tract acting separately or together. My opinion is in harmony with some of Lucas' conclusions which I have combined for this purpose; i.e. "since ureteral peristalsis influences renal circulation and vice versa, there appears to be an ureteral influence in the diuresis caused by some drugs which increase muscular activity and tone of the ureter" The case may be stated more exactly if the upper expanded portion of the ureter and its branches are included

Insertion of a catheter into the renal pelvis of the one kidney to eliminate the influence of its ureter for the purpose of control of volume output, and application of such findings to the other side in which a catheter is placed in the lower part of the ureter does not take into account changes which might be produced by muscular structures of the infundibula and calyces, possibility of independent activity of each kidney, nor the possibility of a difference in urinary pH on each side (as I have occasionally found) Muschat has presented histo anatomical evidence of the presence of a smooth muscle so arranged around the renal papilla as to suggest its action in the manner of squeezing or aspiration of the urine from the tubules in the pyramidal tips In urograms are frequently observed contractile states of these upper smooth muscular structures which no doubt partake of the phenomena of systole, diastole and pause The upper urinary tract may be involved in the same muscular phase, or various phases may be limited to sections of the tract (as I have previously pointed out) with consequent changes in rate of excretion and its volume output For these reasons, the method of recording volume output as outlined, is not without objection

Since the kidney is essentially concerned in regulation of the acid-base equilibrium in functional studies of this organ and of urinary tract musculature, it is only logical that the factor of urinary pH be considered, both in relation to its *influence on the essential and other ions and the possibility of its sensitizing the* tissue to the action of particular drugs or chemicals under investigation A number of studies have been concerned with effects of pH on smooth muscle including the ureter (Roth, Andrus, Evans and Underhill, etc) In general these findings indicate that *alkalies* support increase in contractile phenomena and susceptibility to excitation, whereas *acids* decrease irritability, inhibit motor activity or exhibit a tendency in that direction An example of what is thought to be the influence of the pH factor may be seen in the urograms of Diodrast excretion exhibited at this convention In numerous observations from our clinic it was found that the urinary tract including the ureters were far less sensitive to instrumentation when the urine was acid than when it was alkaline

Our comparative investigations (ureteral tracings, urographic studies, clinical *observations in ureteral colic) of calcium were theorized on the basis of its mode* of action in accordance with the work of many able investigators in this field On the basis of Lapides' observations, insufficient in number and without data relative to the state of urinary pH, his finding that calcium is without any effect on the ureter can not be viewed as valid or conclusive They are but in partial agreement There are sound scientific reasons amplified by clinical observation that calcium is a valuable agent for relief of irritability of urinary tract musculature, but its action is contingent upon its proper employment, i e, adequate ionization

There are more variables of importance than our colleague has indicated which no doubt account for not a few variations reported in physiological and pharmacological studies of the ureter.

Simplification, by the assignment of a single though important cause does not always complete the picture-puzzle of complex problems such as are involved in studies of this apparently whimsical organ called the ureter. In my critical analysis I hope I have not denied the importance of Lapides' work, and the import of his observations; postulated conclusions and implications thereof should not be lightly regarded. Certain aspects of this investigation should, in my opinion, be carefully reviewed by others for either substantiation, modification or change, for then the weight of incontrovertible evidence will surely indicate the proper direction.

MR. CAMPBELL BEGG (Johannesburg, South Africa): It is a great privilege to address this meeting, after 20 years, when you gave me the honor of making me an honorary member.

This subject is of vital importance. The physiology of the pelvis, kidney and ureter is a thing we must know, in order to interpret any pyelogram, and that we have to do every day.

I fully agree with Dr. Lapides' statement that peristalsis will carry on, on a myogenetic basis without nerve fibres at all. We know that is true. Every smooth muscle in the body, if nature had to spend itself on sending impulses from the higher centers all the time to keep the body going, would not keep going. The same is true with the intestine.

I don't think we should minimize the value of the parasympathetic and the sympathetic balance all the same. They do not carry on the routine peristalsis. That name, peristalsis, when you come to analyze it, is a very difficult concept, and probably includes a great number of movements, but it does put the ureter and the kidney and the bowel into a posture to work to the greatest advantage for the circumstances that exist at that moment in the body.

That is a lesson that I find the greatest difficulty in driving home to students, that the cadaver which is lying, probably died on its back, and lying in the tank for a few months, the cadaver which he dissects does not show anything like the movable anatomy of the human body, which is adaptable to one hundred phases —for example, the athlete jumping over a high pole, the football player going down to make a tackle, or the diver, diving down in the water under several atmospheres pressure. In a person lying on his back, with his feet in the air or head in the air, the ureter and whole excretory apparatus of the kidney have a totally different problem to solve.

When the patient has not had water for some time, we cannot consider that picture we see as at all typical of the many features of the ureteral pelvis, as I said in the paper published last December.

This is often misunderstood, by thinking that the ureter, by taking one drop at the top and running it down and then another drop and running it down, and another drop and running it down, is going to be able to cope with every phase of the work it has to do. That is rather ludicrous.

If that were true, then the appearance that we see on pyelograms would have no meaning at all, because we don't see on the pyelogram a drop of urine half way down, and then another drop of urine half way down We see the ureter divided into segments, with one part filled and another not filled, and a thin intervening space, and in the next phase the intervening part may be filled

Those who have been in fighting in desert countries, or who have been with troops in desert countries in hot weather, know that urination is a very minor part of life It is usually toward the afternoon, when subjected to a temperature of 130 and sweating all day, he may pass, if he remembers it, an ounce or two of thin syrup The kidneys only have to cope with about 1 drop every 20 minutes, whereas, after an event such as last night perhaps, the kidney may have to secrete very vast volumes all the time, and therefore, the kidney, in my view, and I am referring to the work of older writers, is not a mere wave mechanism of pushing a drop into the bladder by peristaltic wave It does that sometimes, but if it has to do a big job, it prepares itself for it, because Nature has prepared it by dividing the ureter into a series of boost pumps, and each of these pumps can widen itself

There are two very significant points in Dr Lapides' paper

First, he says that it has been found that the lower segment of the ureter is more active than the upper segment, and everybody knows, who has thought of it, that it is much harder to see the opaque medium in the pyelogram of the lower segment than any other part Why? Because the lower segment, acting independently, is emptying it You can not have a difference of rhythm in a long tube If it starts at a certain rate, it has to go through at a certain rate, or dam up That is one point

The second is that with a great volume of water, a great volume of excretion, pressure increases but peristalsis fails In other words, you are dealing with a wide tube which is emptying itself, not undergoing peristalsis

That to my mind is the only possible way to interpret pyelograms If you think that the ureter consists of a series of, shall we call them cystoids, with a sphincter and a detrusor, then half this talk which was lived on and which I was brought up on, of angles and kinks, dilatations and strictures as pathological, are just in the discard They are physiological phases in order to overcome pressure, to deal with the polyuria, increased volume, or for other purposes, and if they are taken on as a determining pathological cause, numerous operations for angulation and other things will be done, for things which are purely physiological

Therefore, I want, finally, just to emphasize the actual practical *importance* of this matter, because if we cannot get a proper conception of the interpretation of pyelograms based on actual and not traditional ureteric physiology, we will be getting into a maze and thinking of a dozen conditions as pathological when they are simply one of the numerous phases through which the ureter and pelvis go in order to adapt themselves to varying conditions

DECAPSULATION OF THE KIDNEY FOR ANURIA DUE TO SULFATHIAZOLE

IRVING J. SHAPIRO

Sulfonamides had been used clinically for only a short time when reports of urinary tract complications began to appear. Instances of hematuria, oliguria, and anuria were reported, and observers stressed the importance of close watch of the urine during treatment. The early reports were concerned almost entirely with the danger of crystallization of the sulfonamides, the resulting oliguria and anuria being caused by the mechanical blocking of the pelves and ureters with masses of crystals. The more recent literature differentiates sharply between the oliguria and anuria produced by mechanical obstruction and that produced by a direct nephrotoxic action of the drug on the kidney tubules, similar to that seen in mercury poisoning. It would seem likely that such a reaction could be one manifestation of an allergic sensitivity, either congenital or acquired, by previous administration of the drug. Such a differentiation is of extreme importance because of the difference in therapy. Ureteral manipulation and pelvic lavage with solutions of alkali are usually effective in breaking up the masses of crystals and relieving anuria. Occasionally pyelostomy or nephrostomy may be necessary because of mechanical difficulties in breaking up the impacted crystalline masses. However, in those cases in which crystals are absent from the urine and in which no urine is obtained by passing ureteral catheters up unobstructed ureters into empty pelves, we must assume primary tubular damage, and the prognosis in such cases is a much more serious one. Such cases are the subject of this report.

CASE REPORTS

A white man, 27 years of age, entered the hospital on July 8, 1946, complaining of fever of 2 days' duration. He had been sun bathing on July 4 and felt a little warm the next day. On the evening of July 6 he felt "groggy," and his temperature was found to be 103 degrees. A physician was called who prescribed 1 gm. of sulfathiazole and 2 gm. of soda bicarbonate every 4 hours. The patient later began to vomit and have loose stools. The next day he had a chill and his temperature rose to 104 degrees. That night the sulfathiazole was stopped after he had received a total of 6 gm., and penicillin was started. He continued to vomit and had severe epigastric pain. On July 8 he had another chill with accompanying elevation of temperature and was admitted to the hospital.

The patient was a veteran of long service in the South Pacific, during which period he had had 3 attacks of dengue and 1 attack of dysentery. The only other item of significance in his past history was recurring attacks of seasonal hay fever. Examination on entrance to the hospital revealed a temperature of 105.4 degrees, pulse of 128, and respirations of 20. Blood pressure was 125/80. He was a well-developed, disoriented white male with a somewhat reddened skin due to sunburn. The physical examination was essentially negative. He had passed no urine since 2 a.m. of the morning of admission. An x-ray of the chest proved negative. The blood count showed 4,990,000 red corpuscles, 9,500 white blood cells, and 15.8 gm. of hemoglobin. The differential count showed 91 per cent polymorphonuclear leucocytes, 8 per cent lymphocytes, and 1 monocyte. There was basophilic stippling of the red cells. No malarial parasites were seen.

Intravenous administration of glucose and one-sixth molar sodium lactate solutions was started immediately. He voided only 3 ounces of urine in 24 hours. The specific gravity was 1.023, reaction was acid, and albumin was present in large quantities. There was no sugar, but the reactions for acetone and diacetic were positive. Microscopically all fields were overloaded with granular casts. There were only an occasional white and red cell, and no sulfa crystals were seen. The blood chemistry showed values of 52 mg. per cent of urea, 6.5 mg. per cent of creatinine, and a CO_2 combining power of 61.3 volumes per cent. Total proteins totalled 5.1 gm. per cent, broken down into albumin 3.9 and globulin 1.2 There was only a trace of sulfathiazole in the blood.

Cystoscopy was performed at 6 p.m. of the second day of admission. There were 7 ounces of dark urine in the bladder. There was no evidence of crystal formation and the bladder and ureteral orifices were normal in appearance. Catheters passed unobstructed to each kidney, but there was no urine drainage. Both catheters were irrigated with sterile bicarbonate of soda solution and the solution returned tinged with blood. The catheters were left in situ and irrigated every 2 hours during the night. The next morning there had been no urine drainage and the catheters were removed. At 4 p.m. catheterization was productive of 3 ounces of very bloody urine. The patient was toxic and had developed a marked pallor. His temperature was 103.6 degrees and his blood pressure 140/90. There was marked puffiness of the face, arms, and hands. The red cell count had dropped to 3,560,000, and the white count was down to 4,300.

On July 11 catheterization was productive of 30 cc of what seemed to be practically pure blood. The temperature was still elevated and the patient badly disoriented. Blood pressure was 160/90 and the urea nitrogen had risen to 74 and the creatinine to 12. The condition of the patient was deteriorating rapidly and some positive action was necessary to avoid a fatal outcome. At 7 p.m. the patient was taken to the operating room and a spinal anesthetic administered. It was believed that this in itself might have a therapeutic value if there was an element of vascular spasm involved in the anuria. Bilateral renal decapsulation was then carried out as rapidly as possible. The findings at operation were remarkable in two respects. First was the enormous edema of all the tissues. Bloody fluid oozed in large quantities, especially from the subcutaneous and perirenal fat. Second was the markedly swollen, tense condition of the kidneys. They were a dark red cyanotic color, and with the first nick of the capsule by the scalpel there was marked bulging of the underlying renal tissue. The kidney tissue was extremely friable, and because of the necessity for haste and the danger of hemorrhage it was inadvisable to secure a specimen for biopsy. The patient was returned to bed in a condition not much changed from that existing prior to operation. Blood transfusion was considered and rejected because of the possibility of an adverse reaction on the damaged kidneys. Catheterization done at the close of the operation showed no urine to be present in the bladder.

The next morning the general condition of the patient seemed unchanged. He was catheterized and 100 cc of amber urine was found in the bladder. This showed a large amount of albumin with numerous red and white cells. There were no casts. During the day the patient remained quite somnolent and the nurses noted some twitching of the extremities. At catheterization in the evening 180 cc urine were recovered.

The day following was a discouraging one because the total output of urine was only 120 cc, but on the next day, July 14, the output jumped to 960 cc and the patient began to show definite improvement in his general condition. From this point there was continued rapid improvement. The patient was unable to void, so an indwelling catheter was inserted. In spite of the large urine output and the subjective and objective improvement, the blood nitrogen continued to rise and did not begin to recede until 11 days after the operation. The reason for this phenomenon is a little obscure, but it was believed that because of the large amount of nitrogen waste products in the edematous tissues of the body, even with a good urine output, it took the kidneys many days to catch up with the work so long left undone.

The patient was allowed up in a chair on the eleventh day, and made rapid progress thereafter. The wounds healed well, and the patient left the hospital 3 weeks after the operation. Urinalysis was negative, but the specific gravity remained rather low and a moderate secondary anemia was still present.

Case 2. A white male of 55 years was admitted to the private service of Dr. Harry C. Rolnick at Michael Reese Hospital on November 24, 1943. I wish to express my appreciation to Dr. Rolnick for permission to include the case.

The patient gave a history of having developed a left parotitis 10 days before entrance. Sulfathiazole was prescribed and he took a total of about 20 gm. in 5 days, when the swelling subsided and the drug was stopped. On November 21 he had difficulty in urination, and on November 22 he passed only half an ounce of urine, and there was no urine from then to the time of admission on November 24.

The blood pressure was 148/88. There was a loud blowing systolic murmur over the apex of the heart and marked tenderness over both kidneys. Catheterization revealed an empty bladder.

Cystoscopy was carried out on November 25. The bladder was empty. There was edema of both ureteral orifices. The left one was catheterized fairly readily, but the right could not be entered. On irrigation of the left catheter the return flow was tinged with blood but no urine was obtained. There were no sulfa crystals in the fluid.

Laboratory examinations gave a blood count of 4,960,000 red cells, 17,800 white cells, with a hemoglobin of 13.2 gm., or 79 per cent. The differential smear showed 77 per cent polymorphonuclears, 18 per cent lymphocytes, 4 per cent monocyte, and 1 eosinophile. The blood chemistry values were: nonprotein nitrogen 58 mg., creatinine 14.4 and sulfathiazole of 4.0. Total proteins were 6 6 per cent, divided into albumin 3 4 per cent and globulin 3 2 per cent Urine output continued at zero following cystoscopy, and 48 hours later operation was decided on and carried out Under local anesthesia bilateral decapsulation and nephrostomy were done The findings at operation were similar to those in the previous case, with a great deal of edema of all the tissues and marked swelling of the kidneys Nephrostomy showed both pelves to be empty, but tube drainage was instituted nevertheless A section of each kidney was taken for biopsy

There was an immediate response to the operation and the next day the patient voided 450 cc of urine in addition to a large amount of urine drainage from both nephrostomy wounds Unfortunately neither nephrostomy tube could be made to drain and urine drained from around the tubes into the dressings, so that an accurate record of the output could not be made But with a daily bladder output of from 20 to 50 ounces plus the large amount of drainage from the wounds, there was never any question as to the adequacy of the amount

On November 29, forty eight hours after operation, the patient had an attack of acute pulmonary edema There were diffuse moist rales over both lung fields and the cardiac rate rose to 150 It was believed that the edema had been induced by the intravenous fluids, so these were stopped, the patient placed in an oxygen tent, and digitalis was given Under this regimen the patient improved rapidly

Daily analyses showed urine of low specific gravity with large quantities of albumin and many red and white cells On a number of examinations varieties of casts were found, but on only one examination were a few scattered sulfa crystals seen As in the previous case, there was an increase in the nitrogen retention of the blood following operation and the reestablishment of kidney function The nonprotein nitrogen reached its high point of 120 mg on the fourth postoperative day, and was still 86 on the tenth day Also interesting was the rapid development of marked secondary anemia Five days after operation the red count was 2,530,000 with a hemoglobin of 50 per cent As in the previous case, blood transfusion was not done because of a possible unfavorable kidney reaction

The patient became ambulatory on the fifteenth day, but the wounds broke down and he was taken to the operating room on December 14 and a secondary closure of both wounds done The nephrostomy tubes had been removed on the fourth day and urine drainage had ceased completely within a few days thereafter The patient was discharged on December 28 in good condition and with both wounds healed

The pathologic report by Dr Otto Saphir is as follows: "In sections of the kidney stained with hematoxalin and eosin there is some variation in the diameter of the tubular lumina The majority of the cortical tubules are largely filled by markedly swollen lining cells, many of which are vacuolated or frayed. The more dilated tubules are lined by compressed, cuboidal epithelium Within these tubules are occasionally seen eosinophilic or neutrophilic casts and small basophilic concretions "

DISCUSSION

Murphy[1] and his coworkers have recently described fully the pathologic changes that may occur in the kidney due to sulfonamide compounds. They divide mechanical obstruction into extranephric, in which concretions occur in the pelves and ureters, and intranephric, in which concretions occur in the kidney substance. The second large classification is that of toxic intrarenal lesions without obstruction. These are further subdivided into simple tubular degeneration, necrotic tubular degeneration, and glomerular changes. They also describe various combination changes that may occur similar to the changes observed in the second of our cases. The simple tubular degeneration is similar to that seen in mercury poisoning. The necrotic tubular degeneration is seen in combination with severe inflammatory changes similar to that seen in marked idiosyncrasy to drugs. The glomerular changes were seldom seen and they raise the question of a Bright's disease arising as a sequel in the cases that recover. It is interesting to note that 13 of their 14 patients went on to fatal termination and that the 1 patient who recovered underwent bilateral decapsulation.

Peters,[2] in a recent article, emphasizes the part that increased intrarenal pressure may play in the production of anuria. He advises the restriction of fluids in cases of this type, and with this point we are in complete agreement. In both of our cases the water-logged condition of all the tissues was one of the striking things noted at operation. It is logical to assume that in administering large amounts of fluids intravenously in anuria, we are adding to the vicious circle that already exists. The fluid, instead of being excreted by the kidneys, is deposited in all the tissues of the body, and the amount retained by the interstitial tissue of the kidneys serves further to augment the intrarenal pressure, compressing the blood supply and tubules to such an extent that the process can only be reversed by the relief of this increased tension through decapsulation. The intake of fluid should therefore be restricted to the amount that can be excreted by the body as perspiration, through the bowel, and by evaporation through the lungs. Pulmonary edema and cardiac decompensation may occur if this amount is largely exceeded.

One must not temporize in the treatment of anuria due to the toxic action of the sulfonamides. Cystoscopy and ureteral catheterization should be carried out at once to determine whether crystals are the causative factor. Even if these are absent, pelvic lavage with a solution of bicarbonate of soda solution should be carried out. If this is not productive of a cessation of the anuria, bilateral renal decapsulation should be carried out without further delay. Decapsulation carries with it practically no primary mortality, and can be rapidly performed under local or regional anesthesia with comparative safety even in a very toxic individual. Delay can only lessen the opportunity of the kidneys to return to normal function.

[1] Murphy, F. D., Kuzma, J. F., Polley, T. Z. and Gull, J.: Clinico-pathologic studies of renal damage due to sulfonamide compounds. Ann. Int. Med., 73: 433, 1944.

[2] Peters, J. T.: Oliguria and anuria due to increased intrarenal pressure. Ann. Int. Med., 23: 221–236, 1945.

CONCLUSIONS

Two cases are reported in which anuria occurred following the administration of sulfathiazole, and in which the probable mechanism was the toxic action of the drug on the kidney tubules. Bilateral decapsulation was carried out on both cases with prompt cessation of the anuria and ultimate complete recovery of both patients.

Early decapsulation in similar cases is urged, because of the danger that irreversible kidney changes may occur if the anuria persists too long.

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MASSIVE SPONTANEOUS HEMORRHAGE INTO AND AROUND PARENCHYMAL LESIONS OF THE KIDNEY[1]

LEON HERMAN

Evidence of recent or remote hemorrhages of small degree is commonly found at operation in and around various lesions of the kidney. But massive spontaneous bleeding is a rather rare event which may inaugurate, add to, or abruptly change the clinical picture. In the cases to be reported herewith, the initial symptoms were directly attributable to the bleeding, which in one instance caused severe pain and the sudden development of a large mass in the loin as the result of massive spontaneous hemorrhage into and around a large renal lipoma, while in the other, anuria occurred as the result of displacement and compression of the ureter, incident to intracystic hemorrhage in a case of congenital single kidney with multiple cysts.

Fatty tissue, while not a normal component of the renal parenchyma, may occur here as a true neoplasm, or in the form of replacement lipomatosis. These lesions differ widely in pathogenesis, but resemble each other somewhat in both gross and microscopic features. Lipoma is a rare lesion, usually occurring in an otherwise normal kidney, while the fat in replacement lipomatosis takes the place of diseased tissue. In a series of 46 clinical cases of the latter, collected by Kutzmann in 1936, the fat was large in amount and served to replace chronically infected parenchyma, associated in 79 per cent of the cases, by renal stones. The only exception to this rule was reported by Young who found extensive lipomatosis in a kidney free from both infection and stones. No reasonable explanation has been offered for the occurrence of this condition, but whatever its pathogenesis, the diseased parenchyma is replaced by hilar fat until merely a thin peripheral layer of uninvolved kidney tissue remains. The most extensive example encountered by us is shown in figure 1.

In 1938, Roth and Davidson stated that replacement lipomatosis is not as rare as one might expect from the number of reported cases, an opinion based on the demonstration of deposits of fat in 37 kidney specimens in the pathological museum of Ohio State University. But in many of these cases the deposits of fat were insignificant and occurred in association with various types of chronic nephritis.

The occurrence of intrarenal lipoma may be ascribed to embryonic cell rests arising perhaps as suggested by Roth and Davidson from mesodermic tissue, carried into the renal blastema by tubular elements derived from the ureteral buds. These are true neoplasms, and occur in the majority of cases as small round nodules of fatty tissue situated beneath and attached to the renal capsule. These small tumor have no clinical significance and the kidney tissue adjacent to them suffers only from compression. Intrarenal lipoma of clinical significance, of which approximately 16 are on record, are usually large and often so situated as to render determination of their point of origin difficult, or impossible. To the 12 cases reported up to 1941, Robertson and Hand added 2 cases, and since then, Latienda has described a case and added 1 reported by Bengolea in 1922, and apparently overlooked by Robertson and Hand. In some of the reported cases, the condition resembles replacement lipomatosis. With few exceptions intrarenal lipomata give rise to renal pain and in about one half of the cases a palpable mass is to be found in the loin. Hematuria occurs in about 20 per cent of the cases. In the case to be reported herewith, and in 3 of the collected series, severe renal pain could be ascribed to concealed hemorrhage In one of Robertson and Hand's cases there was extensive hemorrhage about the renal capsule and clotted blood was found between the tumor and the kidney substance. Hinz found perirenal hemorrhage of moderate degree, while in a case clinically similar to our own, Nicholson and Gillespie encountered a large mass which had formed as a result of massive hemorrhage in the region of the kidney, a large hematoma in the upper pole of the kidney and extensive subcapsular and intrapelvic hemorrhage. The lipoma in this case, which occupied the upper pole of the kidney, was small, measuring only 2.6 by 3.5 by 2.5 cm.

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

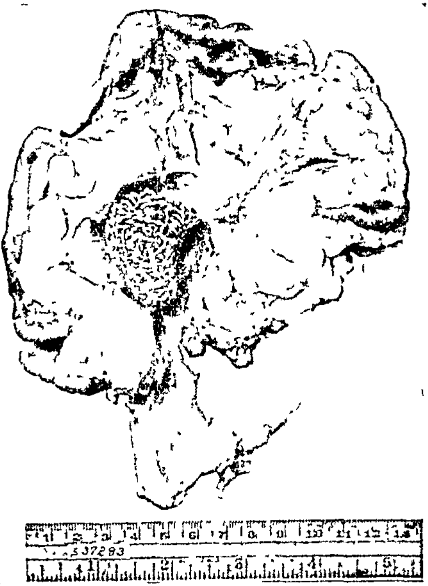

FIG 1. Extensive replacement lipomatosis incident to chronic pyelonephritis with renal calculus. Note thin remnants of parenchyma surrounding fat, which has compressed calyces.

In an asymptomatic case reported by Robertson and Hand, certain parts of the tumor resembled hemangioma of the cavernous type, and many writers remark the richness of the tumoral blood supply. Intrarenal lipomata are usually single and large. Tumors weighing more than 2000 gm. have been reported by Grawitz and Bartsch. In 3 instances multiple tumors were found, while in a case reported by Warthin, the lipoma invaded and filled the dilated renal pelvis and extended down the ureter for a distance of 6 inches, resembling in this particular a case of mixed tumor of the adult kidney, previously described by the writer. The preoperative diagnosis of intrarenal lipoma has not been made. In 2 instances in which the tumors occupied the periphery of the kidney, urographic studies were negative, but in all other cases in which visualization was attempted, there were pelvic deformities more or less characteristic of neoplasm or cyst.

CASE REPORTS

Case 1. Large intrarenal lipoma with massive spontaneous intra- and peritumoral hemorrhage. A. W., a white male aged 54, was admitted to the Pennsylvania Hospital February 3, 1947, complaining of severe pain in the left renal area. This patient, a rugged individual of Norwegian extraction, having retired the night before in his usual state of good health, was awakened by severe pain in the left loin referred to the groin. There was no hematuria. The family physician administered morphine and sent the patient to the hospital with the diagnosis of renal stone.

The patient was pale and complained of weakness and had the appearance of one who had recently lost considerable blood. This was supported by the fact that the blood studies showed only 9 gm. of hemoglobin, 3,300,000 red blood cells and 8,000 white blood cells. The urine and kidney function were normal. A large tender mass filled the loin space and extended to the midabdominal line and midway between the umbilicus and inguinal canal. The overlying muscles were rigid. The umbilicus and surrounding tissues for a distance of one half inch or more were infiltrated with dark blood, a sign of perirenal hemorrhage not observed before by us. The genital tract was normal. The physical and x-ray examinations of the chest showed no abnormalities. Intravenous urograms were interpreted as follows: "Preliminary films show no evidence of urinary calculi. The left side of the abdomen is largely filled with a soft tissue mass, obscuring the kidney shadow. The right kidney is fairly well visualized. In the intravenous study, there is fair visualization of both pelves without gross deformity on the right. There is a gross filling defect with obliteration of the lower calyces and deformity of the lower margin of the left renal pelvis. The appearance suggests a neoplasm or cyst of the lower pole of the left kidney. The ureter is considerably displaced toward the midline at the level of the second and fourth lumbar vertebrae."

On April 5, 1947 the leukocyte count had increased to 12,500 and there was a slight rise in temperature. The tentative diagnosis was concealed hemorrhage occurring in association with a neoplasm or cyst of the left kidney, the presence of pelvic deformity favoring this diagnosis rather than that of spontaneous or so called essential perirenal hemorrhage

Operation (February 6, 1947) Spinal anesthesia was used A transfusion of whole blood was given during the operation. Incision disclosed widespread hemorrhagic infiltration of the tissues and a large black mass filling the loin and extending far downward and inward There had obviously been a massive perirenal hemorrhage and some of the blood had extravasated through Gerota's fascia and into the surrounding tissues After incising the fascia, a large mass of clots was evacuated from the region of the upper pole of the kidney, the latter was freed and clamps placed on the pedicle and the latter cut With the removal of more clots, possibly a quart or more in all, a blood infiltrated yellow neoplasm was exposed, apparently springing from the lower pole of the left kidney The tumor, together with the kidney was removed in the belief that we were dealing *with a hypernephroma which had ruptured spontaneously due to intratumoral* bleeding Recovery was without incident and the patient was discharged February 17, 1947

Pathological report (Dr Crane) "The specimen consists of a kidney, previously opened and partially stripped of its capsule, and attached fatty tissue weighing 340 gm and measuring about 15 by 15 by 5 cm (fig 2) The kidney shows a smooth, brown surface on which are several unilocular, clear cysts up to 0 7 cm in diameter The cut surface shows a red brown cortex 0 5 cm. wide and normally prominent and striated pyramids However, at the lower pole the kidney tissue is flattened and blends with an irregular fatty, yellow mass that has been previously cut and fragmented The capsule of the kidney appears to extend over this fatty tissue and the renal parenchyma is narrowed and distorted with fragments of yellow fat attached to a concave margin of renal tissue This fatty mass extends around the renal pelvis and does not appear to be encapsulated save for the region of the renal capsule Cut surface of this tissue is whitish-yellow and slightly firmer than normal fatty tissue Over the fat there is an irregular coating of red purple blood clot In the fatty tissue in the region of the flattened cortex are 3 round, red nodules 0 2 cm in diameter resembling thrombosed vessels The calyces and renal pelvis are slightly dilated, but not otherwise abnormal There is no communication of these structures with the fatty mass The major branches of the renal artery and vein are normal

"Sections of the main portion of the kidney show normal nephrons and blood vessels At the flattened, lower pole the capsule and compressed nephrons and partially sclerosed glomeruli are flattened over a tissue composed of large clear, adult fat cells (fig 3, *A*). At other points the fat cells extend out to a fibrous capsule, but near here fragments of tubules may be seen in the fat (figs 3, *B* and 4) Closer to the preserved kidney the fat extends directly along the renal border There is no structural wall which would suggest a cyst at any portion Throughout the fat there are large strands composed of fibroblasts and collagen, but no mitsoses or tumor giant cells are noted There are scattered dilated, smaller arteries containing thrombi of fibrin and necrotic red and white cells

"This lesion, as I reconstruct it, is an intrarenal lipoma growing possibly from the peripelvic fat originally, but finally impinging upon and compressing and distorting the renal parenchyma of the lower pole. There are no structures present resembling a clear, cell carcinoma (hypernephroma) or other tumor of the renal components proper. Diagnosis: Lipoma of kidney."

Renal cysts containing blood are commonly found at operation but the clinical picture is rarely inaugurated as the direct result of the bleeding as occurred in the following case.

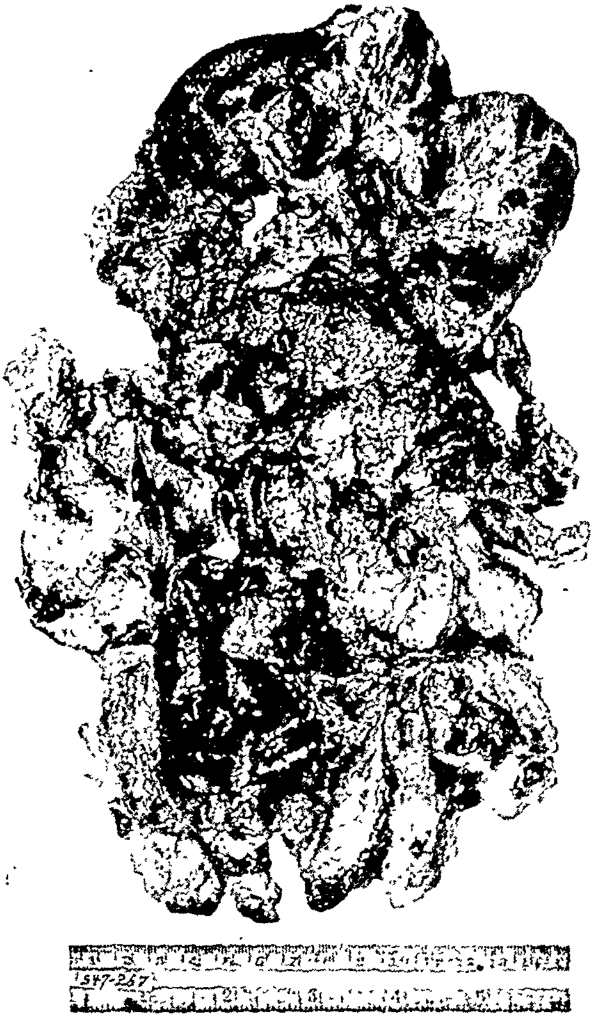

Fig. 2. Section surface of kidney with intrarenal lipoma. Upper two-thirds of kidney are intact, lower third destroyed by blood infiltrated neoplasm.

Case 2. Anuria due to ureteral compression incident to intracystic hemorrhage in a case of congenital single kidney with multiple cysts. Mrs. A. B. H., a white woman aged 64, entered the Bryn Mawr Hospital April 16, 1940 with right costovertebral pain and gross hematuria of 8 days duration. The patient, an obese, hypertensive individual, gave the history of having accidentally swallowed a radium capsule in 1929 which was being used in the treatment of a nasal lesion. The capsule was removed 30 hours later from the distal end of the ileum. The episode was followed by serious illness with hematuria, jaundice, and delirium as prominent symptoms. She recovered after a prolonged convalescence and was in fair health until the present attack.

Physical examination yielded nothing of great importance. There was mild anemia. The urine contained blood but no pus and the cultures were sterile. Kidney function was slightly decreased. Cystoscopic examination on the day of admission showed grossly clear urine. The left half of the trigone was undeveloped, and there were small ecchymoses surrounding the right ureteral orifice. The ureter was unobstructed, and catheterization yielded clear, followed by blood tinged urine. Phenolsulphonphthalein was eliminated from the right kidney in 3 minutes, with a total output of 60 per cent in 2 hours. No dye was recovered from the bladder. It was assumed that the bleeding came from the

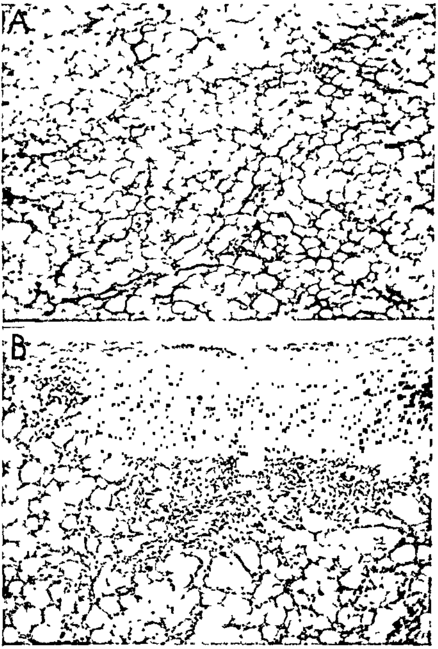

FIG. 3. *A*, Section of tumor, showing it to be composed of large adult fat cells. *B* Section through capsule of tumor. Glomerular and tubular elements are shown between capsule and fat.

right (congenital single) kidney. X-ray examination showed no shadows suggestive of stones. The outline of the right kidney seemed to be much enlarged. The left kidney could not be visualized. Secretory urograms showed faint concentration of the dye after 15 minutes. The right renal pelvis was normal in shape and size. The calyces were indistinctly shown. There was no evidence of a functioning kidney on the left side. A retrograde pyelogram was not done and the patient was discharged, with the condition undiagnosed.

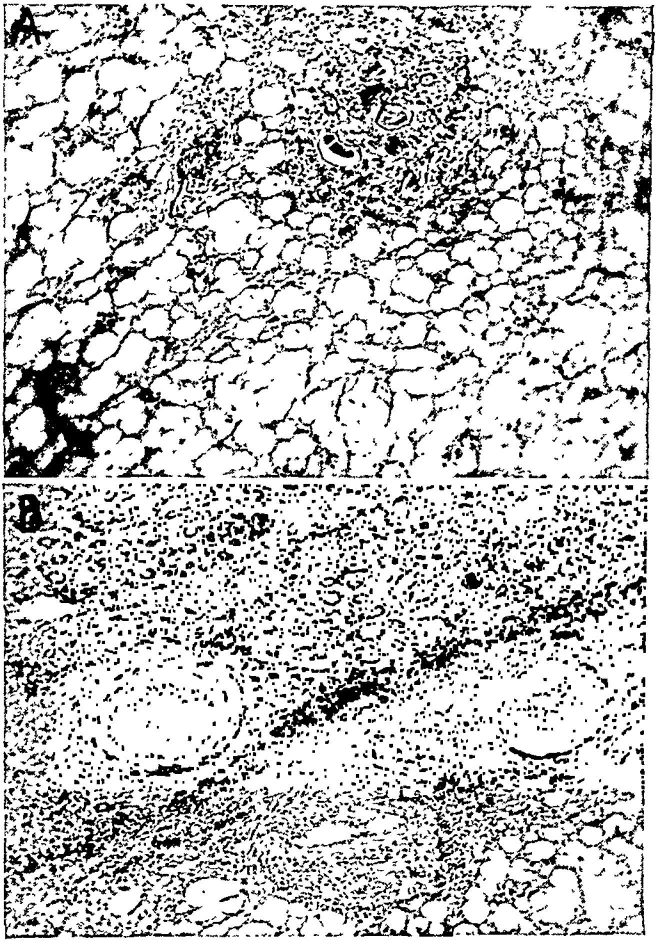

FIG. 4. *A*, Area of tumor, showing small group of atrophic tubules. *B*, Section of tumor at junction with kidney cortex, which is flattened. There is increase in fibrous tissue and tubules are atrophied.

The patient was re-admitted December 18, 1941. She had had no further symptoms referable to the urinary tract until 2 weeks previously when she noticed dimness of vision and inability to concentrate her thoughts. Suddenly at 11 p.m., approximately 36 hours before admission, she experienced an attack of severe pain in the right costovertebral angle. By the next morning she was semi-stuporous, anuric and obviously very ill. The family physician who shared our belief that there was a neoplasm involving the single kidney reported the circumstances to us, and the patient who was now comatose was immediately brought to the hospital and taken to the cystoscopic room. A No. 5 catheter met no obstruction in the right ureter and more than 60 cc concentrated blood tinged purulent urine was aspirated from the pelvis. The catheter was left indwelling and during the following 36 hours, drained 500 cc urine, when it was accidentally removed. The catheter was replaced 6 hours later. No urine was secreted in the interval. Again there was pelvic retention without demonstrable ureteral obstruction. Large quantities of glucose solution and plasma were given and in the following 12 days the catheter drained well with a daily output averaging about 1500 cc. Strangely enough the highest urea nitrogen blood content was 49 mg. per cent. There was moderate anemia and marked hypertension.

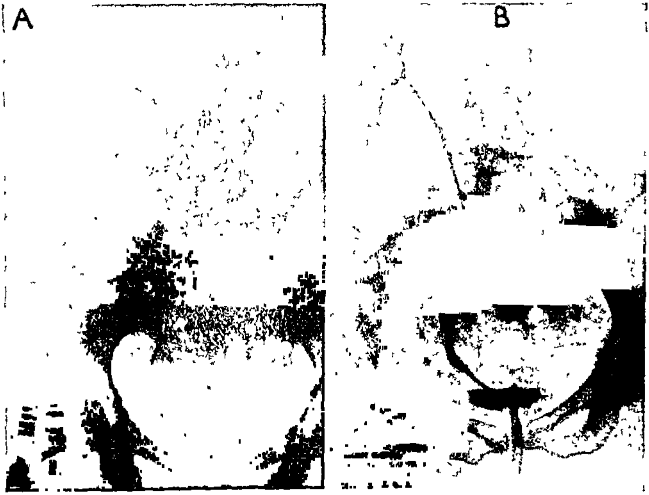

FIG. 5. *A*, Forward and inward displacement of ureteral catheter by renal cyst. *B*, Hydronephrosis with anuria due to ureteral occlusion by large renal cyst.

The eye ground examination disclosed advanced toxic amblyopia; it was not until several weeks after operation that normal vision returned. Improvement was unusually rapid and 3 days after admission the kidney secreted a total of 17.5 per cent phenolsulphonphthalein in a 15 minute period. Plain x-ray studies showed no evidence of urinary calculi. Stereoscopic views with the catheter in position showed marked forward and moderate inward displacement of the latter which after passing far forward, dipped backward to enter the kidney pelvis (fig. 5, *A*). This was confirmed by retrograde pyelograms which also showed that the kidney was displaced downward and outward and rotated so that the ureteropelvic junction was directed forward and inward (fig. 5, *B*). The pelvis and calyces were uniformly dilated but without other deformity. However, it seemed obvious that we were dealing with a retroperitoneal mass which had arisen either from the kidney or from tissues adjacent to this organ and it seemed reasonable to attribute the anuria to pressure on the ureter from without. We did not suspect the occurrence of intracystic hemorrhage.

Operation (December 29, 1941): The lower half of the kidney was exposed through a loin incision. On the exposed portion of the rotated kidney a cyst, 3 cm. in diameter, and 3 smaller ones in size were found and incised. A very large black mass with the ureter crossing it, covered the lower pole of the kidney and extended far forward. This was found to be a blood filled cyst originating from the mesial side of the lower pole of the kidney. The cyst was incised and several ounces of heavy clots evacuated, whereupon the ureter filled promptly and the pelvis emptied itself. A large cigarette drain was placed in the cyst and the wound closed. We removed only a small portion of the clots fearing activation of the bleeding, nor did we consider excision of the cyst justifiable under the existing circumstances.

Recovery was slow but fairly uneventful. The patient was discharged from the hospital January 26, 1942, and has had no further trouble referable to the urinary tract. The case is in our experience unique and I have failed to find a similar one among the cases reported under the title "Acute Hemorrhagic Cysts of the Kidney," by Munger and others.

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MALIGNANT ADENOMA OF THE KIDNEY[1]

ROBIN PEARSE

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The following history is of a woman with a large adenoma of the kidney

The patient, aged 58 years, was admitted to the hospital on January 24, 1917 complaining of gradually increasing weakness of 5 years duration   During thi period she had lost 35 pounds   For the past 3 years she also had attacks o dyspnea accompanied by a pounding feeling in the heart, sudden in onset, subsidence gradual, and a sore red tongue

Following one of the recent attacks of dyspnea the patient noticed a peculia feeling in the left upper abdominal quadrant, and on examination her physicia felt a mass, which he took to be a large kidney and referred her for investigation Patient had no urinary symptoms

Examination disclosed an afebrile, pale, thin woman with dark circles aroun the eyes, striae at the corners of the mouth and a bright red tongue with a irregular surface, heart slightly enlarged, blood pressure 140/80 and a pulmonar systolic murmur present

A slightly tender movable mass could be felt in the left, upper abdomina quadrant, suggesting a moderately enlarged lower pole of the kidney

The urine was negative, Wassermann negative, nonprotein nitrogen 29 hemoglobin 90 per cent, red blood cells 4 3, white blood cells 7 5, color inde 1 05   Blood smears showed slight generalized macrocytosis, platelets plentiful

Cystoscopy showed a normal bladder   Retrograde pyelograms showed normal right kidney (fig 1)   On the left side the lower calyces were flattene and curved to the shape of an inverted saucer by pressure from a large spherica mass in the lower pole of the kidney (fig 1)

A tentative diagnosis of parenchymal carcinoma was made and the patient prepared for transperitoneal nephrectomy   In the interim the sore tongue and ora striae disappeared following intramuscular injections of vitamin B complex

Operation   Anesthetic, spinal nupercaine   The abdomen was opened by a incision through the mesial third of the left rectus muscle, extending from just above the costal cartilage down to the level of the umbilicus   The descending colon was retracted to the right and the posterior peritoneum opened along the white line   The anterior layer of the perirenal fascia was torn through and the tissues retracted to the midline   This exposed a large tumor in the lower pole of the kidney   The ureter, which was very small, was divided   A large artery entered the upper pole of the kidney   The renal vein was very large and beneath it could be felt a small artery   After dealing with the blood supply, the kidney was removed, the posterior peritoneum repaired and the abdomen closed, peritoneum, muscle and fascia united by a series of figure of eight wire sutures and the skin by continuous dermal

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[1] Read at annual meeting, American Association of Genito Urinary Surgeons, Absecon, N J, June 4, 1917

The patient made an uneventful recovery and went home on the fifth post-operative day.

Pathological report (W. L. Robinson): The kidney measured 14 by 12 by 8 cm. (fig. 2). The external surface was pale brown in color, and there was a marked enlargement of the lower pole so that the lower four-fifths of the kidney was spherical in shape. This sphere measured 12 cm. in diameter. On opening the kidney a large encapsulated mass was seen, measuring 10 by 7 cm. The mass was situated mainly in the lower and central portions of the kidney. There

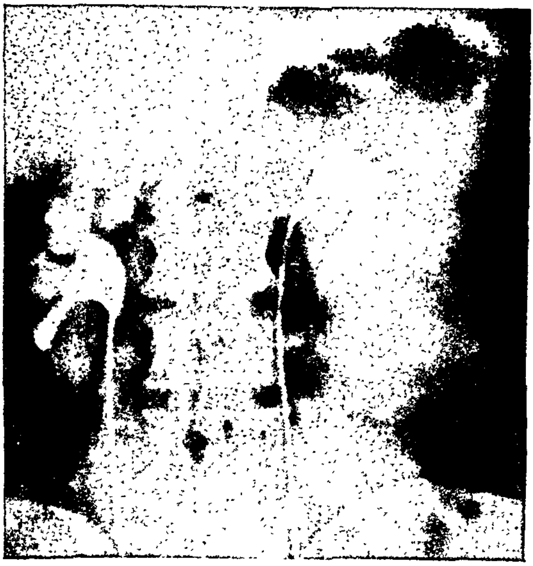

Fig. 1. Urogram

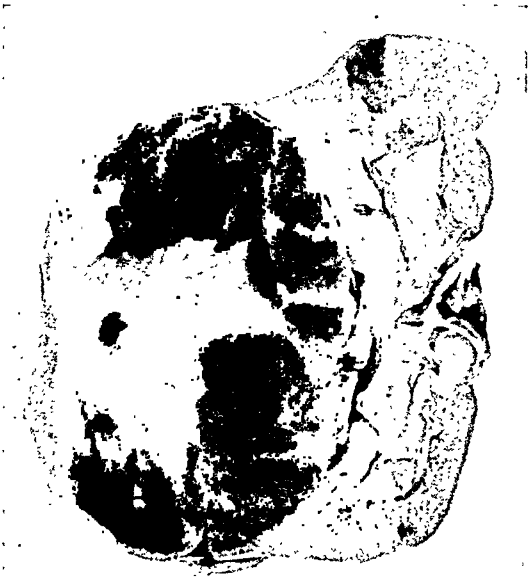

Fig. 2. Hemisection of kidney

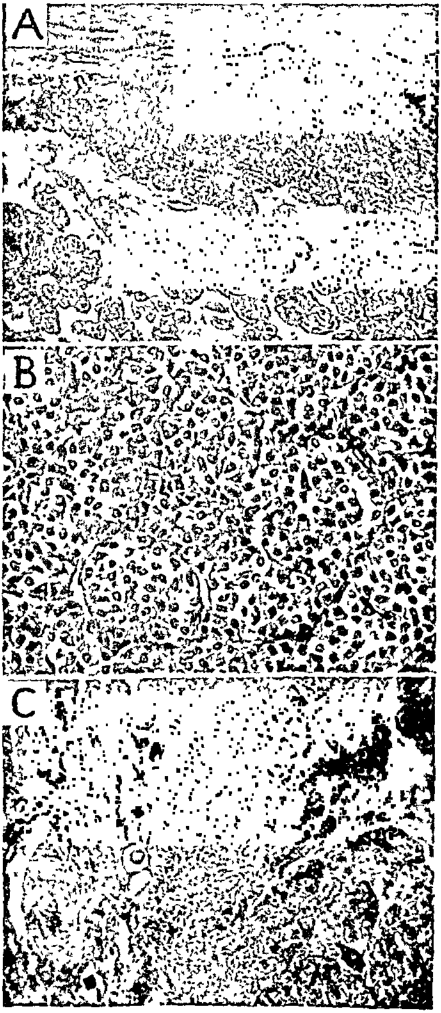

FIG 3. *A*, Benign portion of tumor, low power. *B*, Benign portion of tumor, high power. *C*, Malignant portion of tumor

was a small piece of normal kidney at the lower pole and a somewhat larger piece of normal tissue at the upper pole.

The tumor itself had a central, very firm, gray-white area, which spread in a dendroid manner into the surrounding tumor tissue. This surrounding tumor tissue was brownish red in color, in many places resembling normal kidney tissue. Except for a few submucous hemorrhages, the pelvis was normal. The ureter was extremely narrow.

The tumor presented the histological features of a solid type of adenoma. It had a definite fibrous tissue capsule. The component cells, for the most part, were uniform in size and shape, and possessed a moderate amount of pink-staining cytoplasm with compact, dark-staining nuclei. In some areas the cells had a tendency to form acini but, for the most part, they were growing in solid cords separated by a delicate connective tissue framework. In the center of the tumor were degenerative changes comparable to those frequently seen in thyroid adenomata, such as atrophy of the epithelial elements and replacement by a very loose-textured connective tissue stroma with, here and there, small areas of hemorrhage.

The tumor showed certain malignant characteristics, in local invasion of its own capsule, and areas where the cells were quite atypical in character, as indicated by variation in their size, shape and nuclear staining qualities. See figure 3.

EXTENSIVE METASTASIZING HYPERNEPHROMA ASSOCIATED WITH MASSIVE BILATERAL ADENOMA OF THE ADRENAL[1]

JOHN A TAYLOR

The subjects of bilateral adrenal adenoma and hypernephroma per se have been well discussed and little of interest can be added The association of the three lesions in a single case, with a diagnostic problem, together with added data in connection with the Grawitz theory of adrenal rests is worthy of consideration

Howze, in a report of a case of bilateral adrenal adenoma with a review of the literature in 1942, found 66 cases In all of these cases but one, the tumors were found at autopsy The same was true in this case, it being one of the asymptomatic cases described by Cahill in his presentation of adrenal tumors

The most interesting phase of this case was the circumscribed tumor contiguous with the right adrenal adenoma This tumor was soft and reddish gray in color, and friable, in contrast to the yellow, firm, cortical tumor Microscopically, it was composed of large clear cells which could have arisen from renal parenchyma or an adrenal rest It is typical of hypernephroma Whatever its origin, we are dealing here with a so called hypernephroma growing side by side with massive adrenal hyperplasia

CASE REPORT

*A 54 year old male was admitted to the Hospital for Special Surgery on Sep*tember 13, 1943 He had no complaints until he fell while working 10 weeks before This injury proved to be irrelevant Pain developed in the left buttock, radiating down the leg He had been treated in another hospital for sciatica with diathermy, massage and rest, without benefit, and was transferred because of increasing pain and disability

There was marked limitation of the motion in the left hip There was a lump over the sixth rib The pain was relieved somewhat by traction Blood count showed 4,000,000 red blood cells with 80 per cent hemoglobin, 9,300 leucocytes with 70 per cent polymorphonuclears The Kline test was negative

The blood sedimentation rate was 90 mm in 1 hour

Blood studies (E R Gutman) Serum alkaline phosphatase 4 7 Bodansky units Acid phosphatase 3 8 G units per cent Inorganic P 4 0 mg per cent, calcium 16 2 mg per cent, protein 5 7 per cent

X rays (fig 1) showed extensive destructive changes seen in the left ilium, in the right sacral wings, and there were probably destructive changes in several of the vertebral bodies, notably the seventh and twelfth dorsal and the second lumbar There was considerable collapse of the seventh dorsal body Destructive and productive changes were seen in the sixth left posterior rib The findings were characteristic of multiple carcinoma metastases. Examination of the skull, shoulders, and of the ribs, gave no further evidence of metastasis.

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[1] Read at annual meeting, American Association of Genito Urinary Surgeons, Absecon, N J, June 4, 1947

A genito-urinary consultation was asked to rule out prostatic cancer. The prostate was not suggestive of malignancy and hypernephroma was considered, although the kidneys were not enlarged to palpation. Cystoscopic studies were precluded because of the extensive vertebral involvement with paraplegia which had developed.

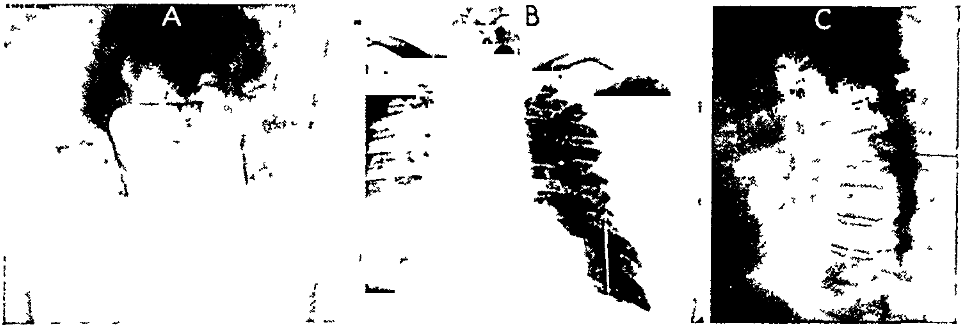

FIG. 1. *A*, Showing destructive changes in left ilium. *B*, Showing destructive and productive changes in sixth rib. *C*, Showing collapse of seventh dorsal vertebra.

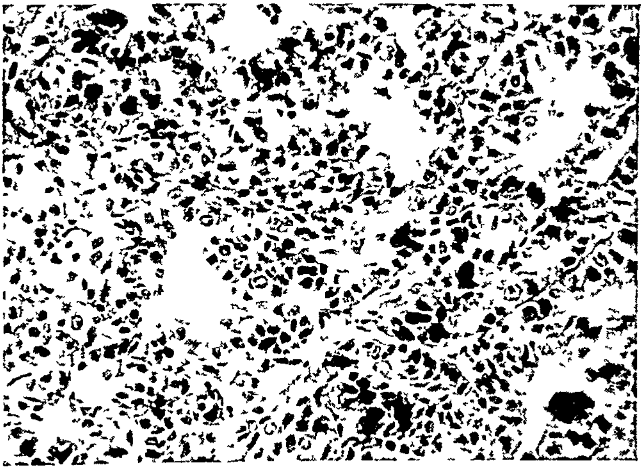

FIG. 2. Biopsy from rib, showing hypernephroma

A biopsy of the lump on the chest wall over the sixth rib and the pathologic study of it showed a very compact overgrowth of cellular tumor tissue interspersed with a few bone trabeculae. The tumor was composed of glandular epithelial cells forming complex, but distinctly papillary structures. These papillae were supported on delicate compressed strands of connective tissue stroma. The tumor cells were characterized by a clear vacuolated cytoplasm and a relatively small vesicular nucleus. The type of cell and papillary pattern suggested strongly that the tumor had originated in the kidney (fig. 2). Diagnosis: Metastatic papillary carcinoma. The probable primary site of the tumor is a hypernephroma or clear celled carcinoma of the kidney.

The patient grew rapidly worse and died on October 10, 1943.

Autopsy (Dr. Milton Helpern): "The body is that of a heavy set middle aged white man, 65 inches tall, estimated weight about 170 pounds. There is moderate obesity of the trunk and abdomen. Scalp hair is black; the eyes are brown; there are several missing teeth. There is purplish postmortem lividity posteriorly. Genitalia appear normal; foreskin present. There is a small granulating surgical incision on the right anterior chest wall 2.5 inches in length. The medial 1 inch of this incision is healed and situated 2 inches about and 1 inch medial to the right nipple. There is moderate swelling of the left thigh with slight shortening and external rotation. There is an area of decutitus on the upper lateral surface of the right thigh. The autopsy was performed through an abdominal incision.

"On section of the trunk, the panniculus is 1 to 2 inches in thickness. The recti muscles are not unusual. The diaphragm on the right is at the level of the fourth rib and on the left at the level of the fourth interspace. The peritoneum is everywhere smooth and shiny except for some fibrous thickening and induration over the descending colon just below the splenic flexure, where a segment of the bowel is found to contain many variable sized inflamed diverticula. These are imbedded in some indurated fat tissue. The liver is slightly enlarged and projects a finger breadth below the right costal margin.

"On opening into the chest, the lungs are found to lie free in the pleural cavities which contain no fluid. No evidence of embolism is found in the pulmonary vessels. The lungs are large, voluminous and heavy. They are crepitant throughout. On section there is considerable edema of the lung parenchyma and also congestion in the dependent portions. The bronchi are not obstructed. They are somewhat thickened and the mucosa is congested. In the visceral pleura of each lung there are several small pearly-gray thin plaques from ⅛ to ¼ of an inch in diameter. There are no metastases in the lung parenchyma.

"The heart lies free in the pericardial sac and weighs 440 gm. There is moderate hypertrophy of the large ventricle; there is also an excess of sub-epicardial fat. The chambers of the heart contain abundant postmortem "chicken fat" clot. The pulmonic valve, instead of being divided into 3 equal sized cusps contains 1 cusp which is subdivided into 2 of unequal size, one considerably larger than the other. The mitral valve leaflets are slightly thickened and the ring calcified. The aortic valve cusps show moderate fusion of the commissures. The tricuspid ring is 4¾ inches and the pulmonic ring 3⅜ inches in circumference; the mitral ring is 4¼ and the aortic ring is 3 inches in circumference. The left ventricle is ¾ inch in thickness. The coronary arteries are patent at their mouths and throughout their course show a moderate amount of eccentric atherosclerosis.

"The myocardium, in section, is brown in color without fibrosis. The aorta throughout its length is somewhat inelastic and in the abdominal portion there are a few calcified plaques.

"The esophagus is natural. In the cardiac end of the stomach, the mucosa is hyperemic. The stomach contains some greenish gray mushy content. The small bowel contains some mushy greenish brown content and the large bowel some mushy greenish brown feces. In the descending colon just below the splenic flexure there is a segment of bowel 3 inches in length which is indurated. On section of this segment of bowel there are several diverticula, the largest of which is 2.5 cm. in diameter. This diverticulum shows evidence of chronic inflammation and is firmly adherent to the surrounding pericolic fat which is also indurated. It is filled with a semiliquid fecal material. The remainder of the large bowel is not unusual. The appendix is present.

"The liver is slightly enlarged, normal in configuration. On section it is reddish brown in color. It contains several small discrete tumor metastases which are gray in color. One of these is seen on the superior surface of the right lobe and another one is found on the posterior surface of the right lobe. These metastases are 1 cm. in diameter. See figure 3.

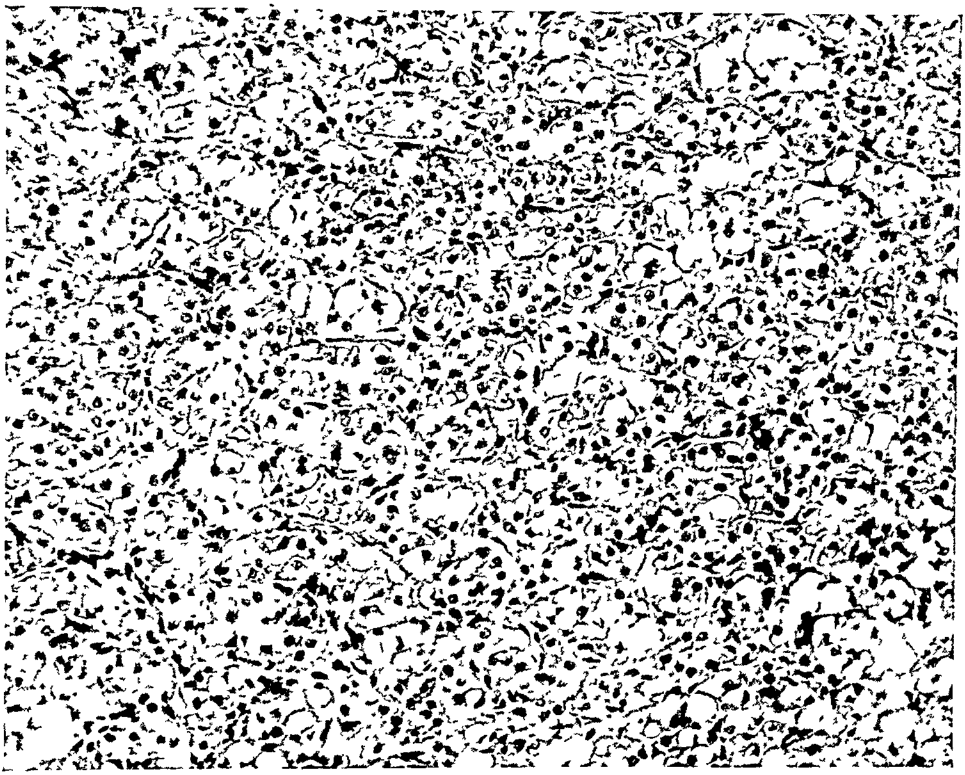

FIG. 3. Metastases in liver

"The gallbladder contains a few cubic centimeters of green bile. There are no stones. The bile ducts are not obstructed.

"The pancreas is normal.

"The spleen is slightly enlarged and soft in consistency. On section, the pulp is red in color. The follicles are indistinct.

"Both adrenals are considerably enlarged and replaced by golden yellow cortical tumor tissue (fig. 4). On each side the adrenals form firm, nodulated broad, thick masses of tumor surrounded by a considerable amount of fat. On the left side, the adrenal measures 11 by 4 by 2.5 cm. On the right side, the solid nodular tumor replacing the adrenal is 10 by 4 by 3 cm. Both adrenal tumors are entirely discrete and separate from the kidneys.

"The kidneys are imbedded in large fatty capsules. The left kidney is normal in size measuring 13 by 6 by 4 cm. The fibrous capsule strips easily. The markings are somewhat exaggerated. The pelvis and ureter are normal. The right kidney is also imbedded in a large amount of perirenal fat and is 12 by 5 by 4 cm. There is a circumscribed tumor projecting from the hilum of the right kidney and situated more in the lower half. This projecting tumor appears to be encapsulated and measures 4.5 by 2.5. On section, this tumor is lobulated and trabeculated, the lobulations varying from 1 to 2.2 cm. in diameter. The tumor tissue, on section, is soft and pinkish and reddish gray in color. It is very

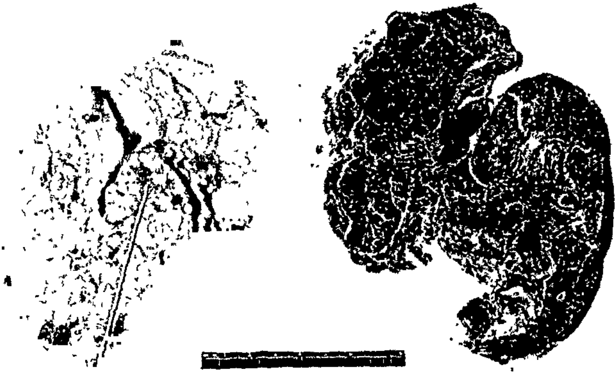

Fig. 4. Metastasizing hypernephroma of right kidney with diffuse adenomatous cortica hyperplasia of both right and left adrenals.

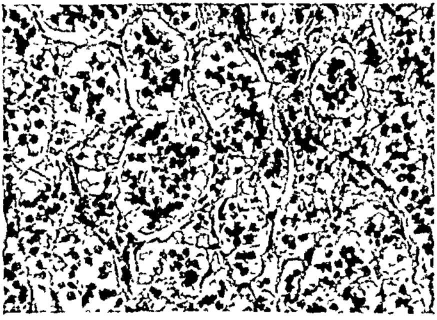

Fig. 5. Adrenal adenoma

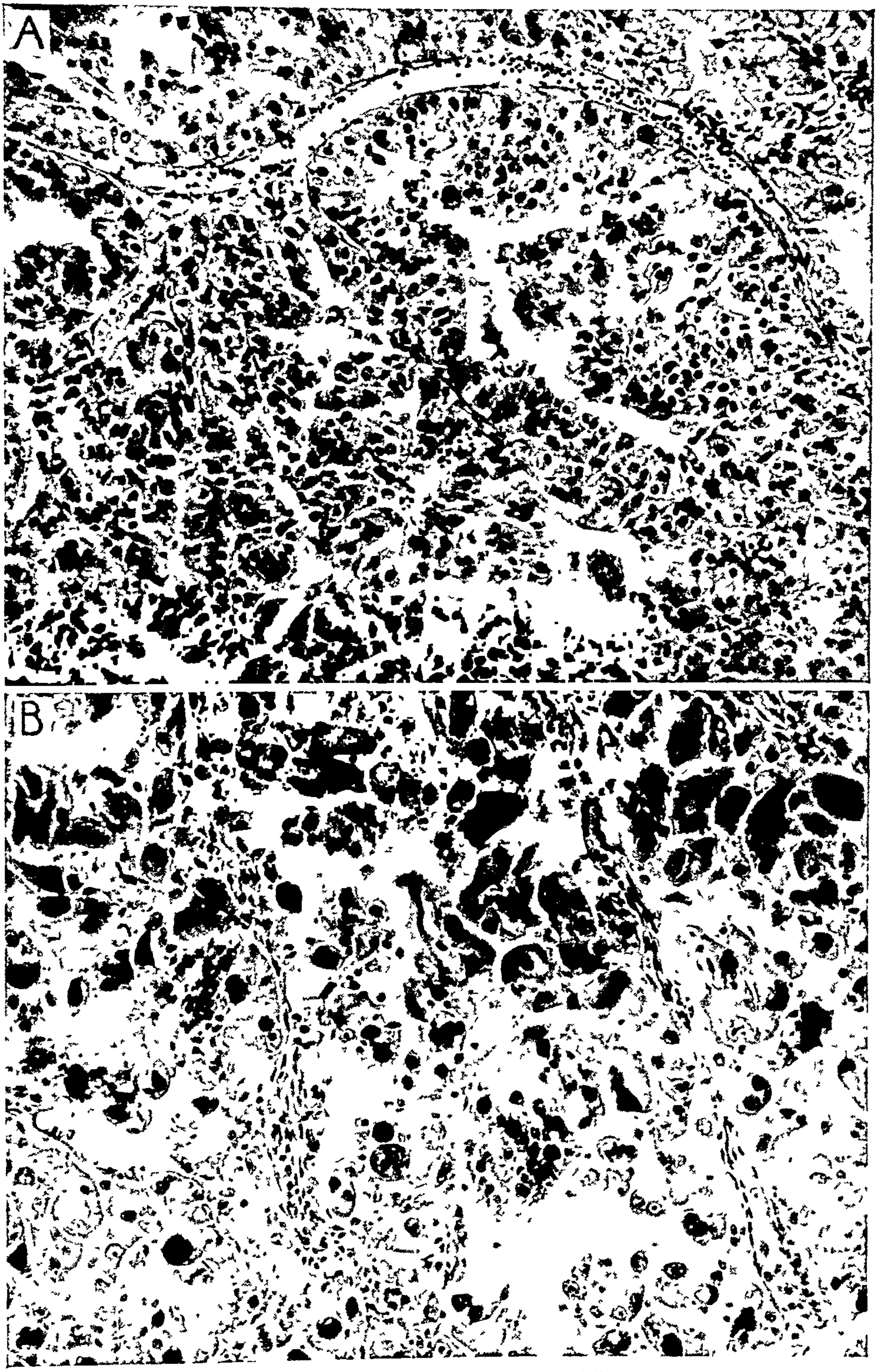

Fig. 6. Hypernephroma, × 375

friable in consistency in contrast to the golden yellow, firm cortical tumors of both adrenals. Grossly there is no evidence of invasion of the surrounding renal veins. The pelvis and ureter of the right kidney do not contain any blood and the markings of the kidney parenchyma are fairly well preserved. See figures 5 and 6.

"The urinary bladder is hypertrophied and the bladder wall is trabeculated. The bladder contains 4 oz. of turbid yellow urine.

"The lateral lobes of the prostate show nodular hypertrophy. The seminal vesicles are normal. The testicles are normal.

"Examination of the left acetabulum reveals complete replacement of that bony structure by soft metastatic tumor tissue, which has completely destroyed and replaced it. The tumor mass is 3 inches in diameter and is readily excised with a knife. When this mass of soft tumor is removed the head of the femur can be palpated through the large defect in the bone. The psoas muscles are atrophied.

"The head is not examined.

"Cause of death: Hypernephroma of the right kidney with skeletal metastases.

"Anatomical diagnosis: Hypernephroma of the right kidney with metastases to ribs (surgical biopsy), left acetabulum and liver; bilateral large cortical adenomata of the adrenals; pulmonary congestion and edema; moderate hypertrophy of the left cardiac ventricle; moderate coronary arteriosclerosis; sclerosis of mitral valve; anomaly of pulmonic valve (4 cusps), atherosclerosis of aorta; diverticulitis coli; recent right headed rib biopsy incision."

SUMMARY

A case of bilateral adrenal adenoma associated with a small clear cell carcinoma which metastasized extensively and caused death is herewith presented.

The writer is indebted to Dr. Francis Carter Wood for the microphotographs.

2 E. 54th St., New York, N. Y.

SPONTANEOUS DISAPPEARANCE OF PULMONARY METASTASES AFTER NEPHRECTOMY FOR HYPERNEPHROMA. FOUR YEAR FOLLOW-UP

LEWIS T. MANN

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Spontaneous disappearance of multiple pulmonary metastases of hypernephroma is rare, but several cases have been reported.

Bumpus described the apparent disappearance of such metastases in the case of a man, aged 59. His patient, who had a negative preoperative x-ray of the chest, developed a cough with bloody sputum and positive x-ray evidence of multiple nodules in the lungs 15 months after nephrectomy for hypernephroma. Five months later, the cough and the pulmonary metastases disappeared spontaneously. Re-examination 3 years later showed the lungs to be clear.

Beer mentioned a similar case with pulmonary metastases appearing after nephrectomy for hypernephroma. The patient developed a cough, and the lungs were found to be the site of multiple large and small nodules radiographically. Five months later, the cough disappeared, and the lungs were found to be clear.

Hyman stated that in his opinion, the presence of metastases is no contraindication to nephrectomy for renal tumor. He performed nephrectomy on several cases in the presence of single metastasis. He mentioned that a number of cases have been reported, where patients have survived for years after nephrectomy and excision of a single metastasis. He also stated that pulmonary and bone metastases of hypernephroma are of such slow growth that nephrectomy should always be given serious consideration.

In addition to the case being reported, we have seen 2 patients with solitary lung shadows interpreted as metastatic tumor by the radiologist. In both instances the shadow disappeared after nephrectomy for hypernephroma.

In the cases of Bumpus and of Beer, the multiple lung metastases appeared after operation, and then disappeared spontaneously. In the case being reported, the lung metastases were present preoperatively.

CASE REPORT

S. B., No. 514000, a male, aged 62, was admitted to the Mount Sinai Hospital on December 7, 1943, with an 8 months' history of progressive weakness, productive cough with dark sputum, and loss of weight. Physical examination revealed a pale, thin, elderly man, with negative findings except for marked secondary anemia. Urinalysis, blood chemistry, and Wassermann reaction were normal. An x-ray of his chest showed multiple metastatic nodules, 1 to 4 cm. in diameter, scattered throughout both lungs (fig. 1).

An intravenous pyelogram, taken in search for a primary focus, showed a mass compressing the calyces of the lower pole of the left kidney, typical of tumor. This was confirmed by retrograde pyelogram.

On December 22, 1943, a left nephrectomy was performed. A tumor, the size of an orange, was found occupying the midportion of the kidney.

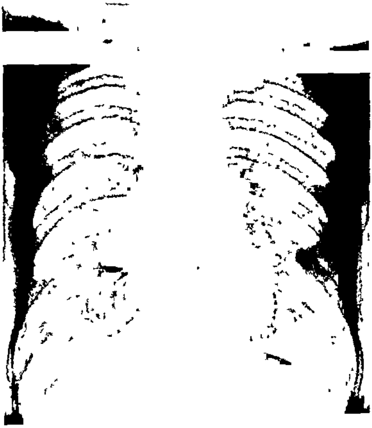

FIG 1

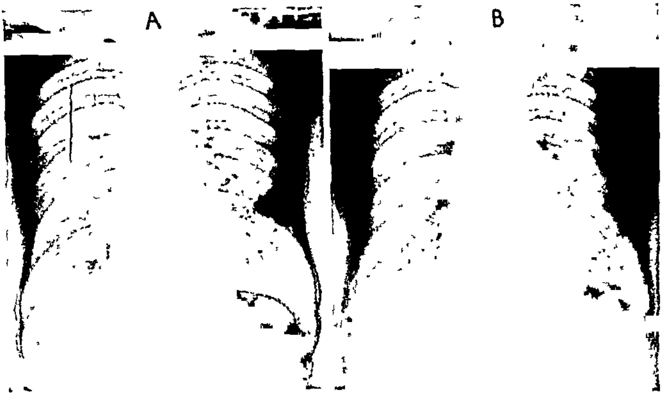

FIG. 2

The pathological report of the specimen was "malignant Grawitz tumor (hypernephroma) with invasion of the small veins and lymphatics."

The postoperative course was uneventful, and the patient left the hospital January 3, 1944, twelve days after operation.

On February 19, 1944, about 7 weeks later, an x-ray of the chest (fig. 2) showed larger and more extensive pulmonary metastases.

On April 1, 1944, the patient was re-examined, and his condition appeared worse. He returned on December 2, 1944, and was found to have gained some weight.

He failed to report again until September 1, 1945, when he stated that he had had cough with frank hemoptyses during the summer, but gained weight. An x-ray of his chest on September 1, 1945, showed complete disappearance of the nodules.

We next saw him on October 6, 1945, when he stated that there had been no further hemoptysis. He appeared to be in better health, and had gained weight.

On April 6, 1946, September 1, 1946, and on October 4, 1947 an x-ray of the chest continued to show the lungs free of metastases. X-ray of the bony pelvis and long bones taken on December 7, 1946 was negative.

Comment: The unusual feature in this case was the spontaneous disappearance of multiple pulmonary metastases of hypernephroma, present at the time of nephrectomy.

In cases recorded in the literature, the metastases appeared postoperatively, with subsequent spontaneous disappearance, or a solitary metastasis was removed before or after a nephrectomy for hypernephroma, whereas in this case the metastases were present before operation.

Why there was a disappearance of metastases is unanswered, and is a topic of speculation.

The patient's progress will be followed, and a supplementary report may shed more light on the subject.

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BILATERAL EMBRYONAL ADENOMYOSARCOMA OF THE KIDNEY (WILMS TUMOR)[1]

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The occasional true primary bilaterality of embryonal adenomyosarcoma or Wilms tumor of the kidney would seem to confirm the congenital nature of the lesion and corresponds to congenital bilateral tumors in other paired organs—the eyes, ovaries and testes Doubtless in many cases thought to be primary bilateral Wilms tumor, the growth on one side represents secondary invasion from an initial unilateral lesion Most reported cases of bilateral Wilms tumor have been found on postmortem examination, rare instances are recorded in the reports of series of renal tumor cases by various authors and to discover these, an enormous mass of literature must be reviewed Ladd encountered it once in a series of 58 cases In 17 cases of Kretschmer and Hibbs, one was true bilateral, another showed late secondary invasion of the remaining kidney. Yet in 44 proved cases at the Mayo Clinic, Weisel, Dockerty and Priestley found none bilateral nor did Dean encounter bilaterality in a hundred cases of Wilms tumor at the Memorial Hospital Children with this condition subjected to bilateral pyelography are indeed rare In Harrison's patient, a 1 year old male, the diagnosis was made by excretory urography and confirmed at autopsy, each tumor-bearing kidney was approximately 12 cm long In 141 cases of Wilms tumor collected from the literature and reported by Walker in 1897, ten were bilateral Yet it seems likely that in many of these "older" cases, the diagnosis is seriously open to question, it having been made chiefly by palpation, polycystic renal disease or bilateral hydronephrosis may have existed It is notable that with more widespread urologic investigation in the young the incidence of bilateral Wilms tumor is strikingly less than that indicated in the literature of the turn of the century A study of the available published case reports since 1930 has revealed those above mentioned and Ueda's case While there are probably some overlooked and several others not reported or not recognized, the condition is still a rarity

Herewith are recorded 2 cases of bilateral Wilms tumor One was subjected to complete urologic examination and the diagnosis was surgically and histologically made, the other was unexpectedly found at autopsy in a 24 day old male The initial interest focuses on diagnosis (possible confusion with polycystic renal, hydronephrotic or adrenal tumor disease) and secondly on treatment.

CASE REPORTS

Case 1 G B, 18 months of age, on October 11, 1946 was referred by Dr Herman Katzman for urologic examination because 1 week previously a large mass had been found in the left side of the abdomen. This mass extended from the costal margin to the level of the iliac crest and nearly to the midline. It was thought that the right kidney was slightly enlarged. The child's previous medical and urological history had been normal. Urinalysis of a catheterized specimen was as follows: yellow, pH 5.5, albumin 1 plus, sugar negative, microscopic examination negative, and culture of the urine was sterile after 48 hours. The blood count showed hemoglobin 8.95 gm. per 100 cc (59.6 per cent); red blood cells 4,070,000 with moderate hypochromia; white cell count 17,700 with 61 per cent polymorphonuclears, 30 per cent lymphocytes, 3 per cent each of eosinophiles, basophiles and monocytes. Roentgenographic examination of the chest was normal except for slight lung compression due to elevation of the diaphragm. Two transfusions of 150 cc each were given with striking benefit.

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[1] Read at annual meeting, American Association of Genito Urinary Surgeons, Absecon, N. J, June 1, 1947

FIG 1

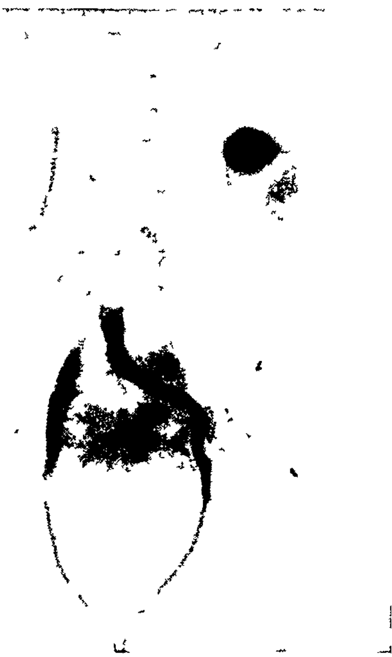

FIG. 2

FIG. 1. Case 1. Excretory urogram, showing a large, dense shadow throughout most of left loin. On right, superior renal calyx is compressed medially and elongated. There is slight downward displacement of middle calyx; lower is normal.

FIG. 2. Case 1. Retrograde pyelography more clearly shows finer right pelvic markings and fails to demonstrate any true pelvis on left.

Just before I saw the boy, an excretory urographic study had been made and showed the shadow of a large mass filling the left loin and no evidence of left renal excretion. On the right the kidney appeared to be slightly enlarged with the lower calyx appearing normal, the middle calyx seemed slightly compressed from above and the superior calyx markedly compressed medially and elongated (fig. 1). Complete urologic examination was then carried out. The left kidney was found to be non-functioning while the right functioned normally as estimated by indigo carmine test intravenously. Bilateral regrograde pyelography showed 2 small round shadows about 1.5 cm. in the region of the left kidney pelvis but no kidney pelvis nor upper ureter as such was delineated (fig. 2). On the right the retrograde pyelography corresponded in general to that seen in the excretory study but the finer markings were more clearly defined

A preoperative diagnosis of bilateral polycystic kidney disease was made, the thought being that involvement on the left was universal and the tumor at the superior pole of the right kidney might be a solitary or multilocular cyst since there appeared to be no change in the lower half of the kidney (fig 1) It was decided to perform left nephrectomy first with subsequent excision of the cyst at the superior pole In bilateral renal malignancy, treatment offers scant hope yet it seems that even should these renal lesions be found malignant, resection of a kidney showing a relatively small amount of involvement offers an exceedingly long chance which should be taken

On October 23 the left kidney was explored through a curved loin incision. Palpation of the pedicle did not suggest vascular invasion by the tumor nor were adjacent involved glands found by palpation The renal surface at once indicated the lesion to be tumor rather than polycystic disease but the surface of the organ seemed much more pale than we are accustomed to observe in Wilms tumor The kidney was removed with some perirenal fat A small cigarette drain was left in the perirenal space, the fascia and muscle were closed with double layer chromic suture, the skin and superficial fascia were closed with interrupted dermal sutures The child's convalescence was stormy but he was returned home on the ninth day

Pathologic Report (Dr John L Work) On immediate gross section of the removed left kidney, the tissue resembled a uterine fibroid or a renal rhabdomyosarcoma It presented none of the brain like type of tissue so commonly observed in Wilms tumor

Microscopic Description "Sections made immediately for the purpose of preliminary identification of the tumor, fixed in formalin and Helly's fluid and stained with hemotoxalin and eosin show the tumor to have a peculiar, fairly characteristic structure Scattered here and there throughout the growth are rather well developed, tortuous, tubular and acinar like structures which are lined by tall cylindrical cells These have deep staining, finely vesicular nuclei, which are generally situated in the bases of the cells These tubular structures are surrounded by broad zones of closely packed embryonal cells, the nuclei of which are not essentially different from those of the cells forming the tubules Both in the epithelium of the tubules and in the undifferentiated cells which surround them, there are frequent mitoses The islands of undifferentiated cells and the tubules in their centers are in turn separated by bundles of fairly loose spindle cells, thus giving the growth a distinct lobular structure In the center of some of the dense, cellular islands there are small foci of necrosis There is no recognizable skeletal muscle, cartilage, or bone in the sections Diagnosis: Congenital mixed tumor of the kidney (Wilms tumor)"

Gross Description: "The specimen in formalin consists of a large lobulated mass which can be recognized as kidney only by the presence of a ureter It has been previously bisected It measures approximately 12 by 12 by 11 cm over all and weighs 656 gm The external surface is ragged, and is partially covered by fat Beneath this there is a tense capsular-like layer in which there are numerous compressed, but otherwise prominent blood vessels. The original section and subsequent sections show the kidney to be almost completely replaced by an abnormal growth. This forms numerous large lobules which vary from 3 to 7 cm. across. Their cut surfaces bulge markedly, are soft, pale yellow to white, and fleshy. In the centers of some of the large lobules there are retracting, translucent pink areas which are somewhat fibrous in character and from which delicate fibrous tenules radiate. In the centers of some of the lobules there are foci of necrosis and hemorrhage. The tumor appears to have originated in the superior and lateral portions of the kidney and has severely compressed what remains of both superior and inferior poles. The growth has broken into the superior calyx, which it has greatly distended. The lining surface of the calyx is covered by delicate polypoid and papillary tufts, some of which are pale and like the rest of the tumor. Some of these are dark red. The tumor has also broken into the middle calyx, this structure being filled by a large oval mass measuring approximately 6 by 4.5 cm. Where kidney tissue can still be identified, the normal structure is lost and the substance is abnormally pale. The inferior calyx is filled with clotted blood and with tumor which has grown downward from the other two calyces. The pelvis is almost completely plugged with tumor. The portion of ureter removed with the specimen measures 3.5 cm. in length and 0.8 cm. in diameter. It is plugged downward as far as the clamp mark with tumor which has obviously grown downward from the pelvis. The blood vessels have been cut close to the hilum. None of them, however, is grossly plugged with tumor."

Microscopic Description: "The original sections prepared for the preliminary report and additional sections fixed in formalin and Helly's solution and stained with hemotoxalin eosin, Van Gieson stain, and reticulum stain show a growth as described in our preliminary report. In the reticulum stain there is very little reticulum in the islands of embryonic tissue. There are delicate fibers, however, in the connective tissue septa between these. Van Gieson stain shows practically no smooth muscle in the tumor. Multiple sections taken through the hilum and including portions of the walls of the major calyces show tumor to have grown into the mucosa giving rise to large blunt irregular processes on the surface. Some of these are covered by compressed transitional epithelium which is continuous with that lining the calyx beyond the tumor-infiltrated portion. There is obvious compression of the kidney tissue adjacent to the tumor. There is edema in the supporting connective tissue and there is atrophy and disappearance and sometimes fibrosis of the glomeruli and tubules. None of the blood vessels included in the sections are filled with tumor. A longitudinal section taken through the tip of the ureter shows stretching of the wall and compression of the mucosa. There is no actual invasion of tumor into the wall. The growth in the lumen is not attached to the mucosa, and fell out during the section process. Diagnosis: Congenital mixed tumor of the kidney (Wilms tumor), with extension into the calyces, pelvis, and ureter."

After a rest of 3 weeks during which the boy received two transfusions, he was returned to the hospital. The right kidney was explored through a curved loin incision. This disclosed the superior polar involvement to be neoplasm which had nearly trebled in size since the boy was first seen and now comprised more than three fourths of the renal mass. Intraperitoneal exploration failed to disclose any tumor-bearing glands and the pedicle was not grossly involved. Having found the right kidney to be malignant it was replaced and the wound sewed up. The boy was returned home after 8 days where his course has been regressive with increased tumor growth and failing nutrition. Largely at the insistence of his father, roentgenotherapy was intensively but ineffectively given for 4 weeks. Six months postoperative the boy is miraculously still alive though death is imminent.

This case has been reported because of its rarity and because of the diagnostic difficulty in which, on the basis of chance together with the bizarre urographic findings, the lesion was thought most likely to be congenital cystic disease rather than bilateral renal neoplasm. It also emphasizes our therapeutic helplessness. To the writer it seemed that the only hope lay in possible resection of the upper half of the remaining right kidney since the lower half represented the only functioning renal element and, had the disease been cystic rather than neoplastic, the contemplated procedure conceivably might have been successful. Radiation therapy is excluded for obvious reasons, any therapeutically effective dose would have destroyed the remaining secreting parenchyma of the child's only kidney.

Case 2. B. O., a 24 day old white male infant, died of inanition. A postmortem examination was made December 7, 1926 at the New York Nursery and Child's Hospital. The important findings were dextrocardia, transposition of lungs, stomach (small), caecum, colon, spleen and pancreas. Both adrenals were absent. Each kidney was enlarged and showed both grossly and histologically embryonal adenomyosarcoma with associated polycystic disease. There was no record of metastases.

SUMMARY

Two cases of true primary Wilms tumor are presented and their occurrence appears confirmatory of the congenital nature of the lesion. In the first instance, the preoperative diagnosis had been bilateral renal cystic disease but the diagnosis of tumor was confirmed by surgery and histologic examination. In the second case, these conditions coexisted with other grave anomalies and were unexpected postmortem findings.

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A MIXED TUMOR OF THE KIDNEY
LIPO-MYO-HEMANGIOMA[1]

NORRIS J. HECKEL AND GEORGE D. PENICK

From the Departments of Urology and Pathology of the Presbyterian Hospital of Chicago, Ill.

Benign tumors of the kidney usually produce very few symptoms unless they attain considerable size, and then the symptoms are usually those of pressure. Exceptions to this rule are hemangiomata and papillomata of the renal pelvis. These two types of tumors may produce such severe hematuria that prompt nephrectomy is necessary. The following case report is unusual in the onset of the symptoms, the gross appearance of the tumor, and the histological pattern of the neoplasm.

Mrs. A. B., a housewife, aged 47, entered the Presbyterian Hospital on August 18, 1946, because of an acute attack of sharp pain in the left costovertebral region of 6 weeks' duration. The pain had occurred suddenly, did not radiate, and could be relieved by the application of heat. During the following 3 weeks, the character of the pain changed to a constant dull ache. There had been no other symptom. The urine had never been bloody. She had always been in good health until 1 year previously, at which time a fibroid was removed from the uterus. She had made an uneventful recovery from this operation. Her weight had not varied in the preceding 5 years.

Physical examination on admission to the hospital revealed a well-nourished and healthy appearing woman about 45 years of age. The temperature was 99.0° and the blood pressure was 112/70. The head, neck, chest, and heart were within normal limits. No masses were palpable in the abdomen. Neither kidney could be felt. However, tenderness could be elicited on bimanual palpation of the left costovertebral region. There was no inguinal adenopathy. The extremities and superficial reflexes were normal. The hemoglobin was 13.9 gm. per 100 cc of blood; red blood cells 4,300,000; white blood cells 7100 per cu. mm. Urinalyses were negative on two separate occasions. Cultures proved the urine to be sterile. X-ray films of the chest were normal with clear diaphragm shadows. However, the plain x-ray film of the genito-urinary tract revealed the left kidney outline to be enlarged. Excretory pyelograms revealed a marked dilatation of the upper minor calyx, with some distortion of the upper and middle major calyces of the left kidney. The right pyelogram was normal. A left retrograde pyelogram (fig. 1,*A*) which was made several days later, confirmed the changes seen in the excretory pyelograms. Cystoscopic examination revealed a normal bladder.

From the above evidence the diagnosis of a left renal tumor was made. A left nephrectomy was performed through a left loin incision 4 days after the patient entered the hospital. No difficulty was encountered in removing the kidney. Examination of the tumor at the time of operation showed it to have all the gross characteristics of a hypernephroma. The postoperative course was uneventful and the patient left the hospital 11 days after the operation. She has since returned to the out-patient department several times. Her last visit was in April 1947, at which time her health was very good.

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

The gross specimen measured 11 by 6.5 by 3.5 cm. and weighed 290 gm. (fig 1., *B*). It was surrounded by adherent perirenal fat. On one surface of the specimen was a tumor 8 by 4 by 4 cm., firmly imbedded in the kidney. On another surface was a previously opened area of cystic degeneration lined by necrotic, hemorrhagic, neoplastic tissue. This cyst was approximately 4 cm. in diameter. Between the cyst and the renal parenchyma was a solid neoplastic mass. The outer surface of this mass was composed of many lobules of yellow or cream-colored tissue. Interspersed throughout the cut surface were septum-like areas of gelatinous, hemorrhagic tissue. The renal parenchyma was elongated and distorted, and extended over the tumor. The latter lay adjacent but not adherent to the renal pelvis. On opening the renal vein no extension of the tumor was found. On cut surface, the renal cortex was tan, and averaged 1 cm. in thickness. The cortical markings were indistinct, and the glomeruli seemed to be irregularly arranged throughout the cortex. The medulla was pink. Smooth gray mucosa lined the renal pelvis. Stripping of the capsule of the kidney was performed with relative ease, revealing a smooth, mottled surface. The fat immediately surrounding the tumor area appeared quite hemorrhagic and necrotic. The impression from the gross examination was that the tumor resembled a hypernephroma.

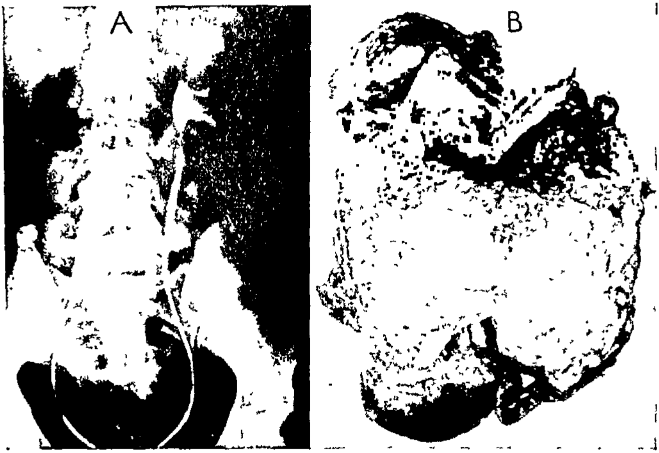

FIG. 1. *A*, Filling defect of left pyelogram. *B*, Cut section of kidney, showing size and relationship of tumor masses.

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

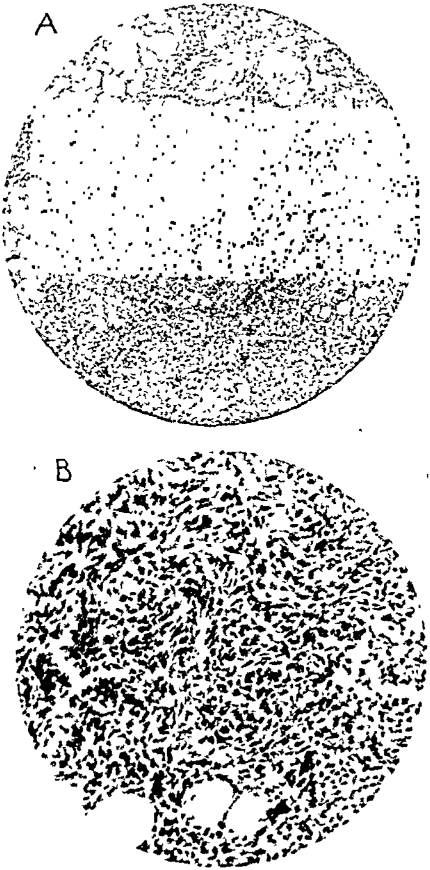

FIG. 3. *A*, Another view of tumor, showing variation in proportion of vascular and stromal components. *B*, High magnification of cellular stroma, showing embryonic character of these cells. Note 3 adult fat cells in field.

calyces dilated, grade 3, with multiple filling defects in the renal pelvis. Catheterization of the left ureter was not possible. As a repeat excretory urogram showed no medium visible, up to and including the 90 minute film, in either renal area, it was believed that the left kidney had little, if any, function remaining. For all practical purposes, therefore, the case had to be considered as one in which there was a solitary kidney. A diagnosis was made of hydronephrosis complicated with a tumor of the renal pelvis. Exploration of the right kidney was advised.

Following the urologic investigation, 500 cc whole blood was transfused as, owing to continuous hematuria, the concentration of hemoglobin had dropped to 4.9 gm. per 100 cc of blood 7 days after admission.

At operation, the kidney was exposed without difficulty through a primary posterolumbar incision. It was found to be hydronephrotic, grade 3, and was enlarged to twice normal size. The ureter was explored and found to be normal. A longitudinal incision was made in the posterior aspect of the renal pelvis and a large, organized blood clot was removed. A papillary epithelioma could then be seen arising from the posterosuperior aspect of the renal pelvis and extending 1 cm. into the upper infundibulum. The greater portion of the tumor was excised along with a small segment of the site of origin. The pathologist reported this tumor to be a papillary squamous cell epithelioma, grade 2 (Broders' method), with no obvious infiltration of the renal pelvis. This being for all practical purposes a solitary kidney, it was not feasible to sacrifice any portion of it. We decided, therefore, that our best method of destroying the lesion and still maintaining adequate renal function would be to electrocoagulate the remaining portion of the tumor thoroughly. This was carried out without difficulty. A nephrostomy tube was placed through the lower calyx and the incision in the renal pelvis was closed.

FIG. 1. Retrograde pyelogram showing hydronephrosis associated with a tumor of the renal pelvis in a solitary kidney

During the first 4 days after operation the patient was given 2,000 cc whole blood in the treatment of his secondary anemia. The urinary output was entirely through the nephrostomy tube and measured 450 cc during the first 4 days. At this time the concentration of urea had risen to 168 mg. per 100 cc blood and the carbon dioxide combining power had dropped to 37.2 volumes per 100 cc plasma. Five per cent solution of sodium bicarbonate was administered intravenously to restore the acid-base balance. The output of urine on the fifth day, and subsequently, never fell below 1,300 cc.

Fourteen days after operation the nephrostomy drainage was clear; erythrocytes were reported as "occasional" and pyuria was graded 1. At this time the concentration of hemoglobin had increased to 10.6 gm. per 100 cc blood, the concentration of urea had fallen to 88 mg. per 100 cc blood, the carbon dioxide combining power was 50.2 volumes per 100 cc plasma and the concentration of protein was 6.7 gm. per 100 cc serum. The patient was out of bed, eating well and feeling stronger than previously.

The patient continued to improve and was dismissed from the hospital on the twenty-eighth postoperative day. The nephrostomy tube was clamped and he voided normally and without difficulty. After 5 days of normal micturition, the nephrostomy tube was removed (forty-fifth day after operation) and the small defect where the tube had been located healed promptly. The concentration of urea was 64 mg. per 100 cc blood and the carbon dioxide combining power was 45.5 volumes per 100 cc plasma. An excretory urogram at this time revealed, as before, no evidence of the medium on the left and absence of renal outline. On the right, dilated tips of the calyces were seen scattered over the large right renal outline. The patient was dismissed on the forty-ninth postoperative day in excellent condition.

Correspondence 8 months after operation revealed the patient to be in excellent health and completely symptom-free.

The prognosis in this case is, of course, guarded. We are well aware that the case is unusual and that the risk attending the procedure was great but we succeeded in stopping an exsanguinating hematuria and possibly effected a permanent cure.

when the diagnosis of carcinoma was made it was believed that radical treatment was indicated.

The addition of these cases of coincident carcinoma of the bladder and chronic interstitial cystitis to those previously reported still leaves the total number very small indeed. However, it is evident that one cannot safely assume that the course of chronic interstitial cystitis is entirely benign. Patients with this disease are frequently treated over long periods of time, and should be subjected to frequent cystoscopic examination in order that the appearance of any suspicious lesions may lead to early biopsy and appropriate therapy for malignancy if it be detected.

29 Bay State Road, Boston, Mass.

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THE ARREST OF HEMORRHAGE OCCURRING AFTER OPERATION ON THE PROSTATE[1]

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Hemorrhage after prostatic operations is usually spoken of as immediate, on the one hand, and delayed, or late, on the other. Each surgeon employs his own preferred methods for the control of immediate hemorrhage. These methods in general rely on four principles: first, ligature of individual vessels; second, mass ligatures, usually in the form of mattress sutures; third, pressure of packs or hemostatic bags and fourth, electrocoagulation of bleeding points. Ligatures must be of absorbable material, and may therefore give way or be absorbed in a few days. The same is true of the so-called absorbable gauze. Vessels, the bleeding from which is arrested by pressure, may start bleeding again at any time. The burned tissue resulting from electrocoagulation sloughs off after a few days, and bleeding may recommence at that time. For these reasons, there is no way in which late hemorrhage can be absolutely prevented; every urological surgeon must know that it is bound to occur in a certain number of cases, and must be prepared to cope with it in an effective manner and at any time.

In 1915, before this Association, and not in a prepared paper, but in the discussion of a paper by another author, Dr. Frank Hinman stated that he had found a practical way to arrest bleeding after the punch operation. His method was to insert a cystoscope, armed with a flexible electrode, and coagulate each bleeding point separately. Unfortunately this statement did not receive wide publicity. I personally commenced to use this method in 1926. Cary Bumpus began independently to use it about the same time, and published a note concerning it in 1929. The discovery directly after this of the report of Frank Hinman's discussion in the Transactions of this Association effectively eliminated any chance of a priority dispute between Cary Bumpus and myself. With the development of the Stern-Davis and the McCarthy resectors, electrocoagulation became the accepted method of hemostasis after all transurethral prostatic resections.

I should now like to offer evidence that electrocoagulation of individual vessels is the best method for dealing with delayed hemorrhage after any prostatic operation, whether it be suprapubic prostatectomy, perineal prostatectomy, or transurethral resection. Methods previously recommended are the use of hemostatic bags, and of packs. Foley bags may be inserted through the urethra, but Pilcher or Hagner bags require cystotomy if the bladder has not already been opened. In the same way, after perineal prostatectomy insertion of a pack or re-insertion of a hemostatic bag requires reopening of the perineal incision.

Experience has shown that with the panendoscope a bleeding artery can be seen at any point in the prostatic cavity, or around its edges. The sole exception would be when the walls of the prostatic cavity had been drawn together by mat-moved on the ninth postoperative day, the perineal incision was entirely healed, and no leakage of urine occurred through it at any time. The patient was discharged as entirely recovered on the twelfth day after operation; that is, 8 days after the hemorrhage.

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

In a personal series of 486 consecutive cases operated upon by transurethral resection, suprapubic prostatectomy, and perineal prostatectomy, there has been no death from hemorrhage. No bladder has been opened for hemorrhage since 1934 (13 years ago). My confidence in the electrocoagulation method has increased to such an extent that I am inclined to intervene early in every case where there is even a fear that bleeding may be of serious moment. This of course is a radical and fundamental change from the previous guiding principle that one should wait until forced to admit that the bleeding was serious. I am convinced that this change of principle is desirable and in fact greatly needed. When it is followed, one no longer sees any exsanguination whatever after prostatic operations. The method is harmless, so that if one occasionally does intervene in a case which might have survived without it, no damage is done.

Death rates have sunk so low in prostatic surgery that the most meticulous attention to detail is necessary, not only to accomplish a desired further reduction, but actually to maintain and preserve the present good situation. A single unnecessary death may double the mortality rate for a whole year. I offer these suggestions for the control of postoperative hemorrhage as a contribution to this meticulous study of detail in prostatic surgery.

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CARCINOMA OF THE PROSTATE: A TWELVE YEAR REVIEW[1]

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During the course of the 12 years from 1932 to 1943 inclusive, the diagnosis of carcinoma of the prostate has been made on 436 patients at the Wisconsin General Hospital. Four hundred cases were used for this study as having carcinoma beyond any reasonable doubt. We have been able to follow 383 cases or 93.7 per cent of the total group.

In undertaking this review we were hoping to find encouragement in the recent methods of treatment. A statistical presentation easily becomes confusing by large numbers of figures. To avoid this contingency as much as possible, discussion of generalities is held to a minimum and our results are presented in a series of charts.

SYMPTOMS

The symptomatology has been repeatedly reported in textbooks and current literature. Our data are presented only as a comparison (table 1). The average age of the patients was 66.1 years; the youngest was 38 and the oldest 93. The average duration of symptoms before admission was 25 months.

The physical findings obviously would depend upon the extent of the disease (table 2). It will be noted that 170 of the cases had metastases at the time of admission.

Table 3 summarizes the methods of treatment used. The 12 years were grouped into 4 year periods to show evident trends. More than one procedure was used on some patients.

Clearly there has been an upward trend in transurethral resections and perineal prostatectomies. The 3 suprapubic prostatectomies were done under the mistaken diagnosis that the cases were benign. Patients with advanced carcinoma prior to 1941, discharged as unfit for surgery, not needing resection or refusing surgery accounts for the large number receiving only supportive treatment (table 4). This group will now completely disappear as they will all have some form of endocrine therapy.

The 1 patient still alive has survived to date 73 months. He has now extensive metastatic lesions causing severe pain in the back and legs. He still refuses treatment. Although the average life span was only 8 months from the time of diagnosis or 33 months from the onset of symptoms, 22 lived much longer. Seven patients survived 9 months, three 12 months, ten 15 months, two 18 months, one 21 months, one 24 months, two 36 months, and one 72 months.

We gained nothing by suprapubic cystostomy (table 5). The average patient lived no longer than the average who received no treatment at all. It is true ual urine as a minimum; their prostates were enlarged, and carcinoma had spread beyond the capsule in many. In some the diagnosis was missed originally and histological examination of the tissue revealed carcinoma.

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 4, 1947.

The 8 patients still alive have lived since surgery 138, 79, 71, 55, 59, 47, 52, and 59 months respectively. Of those who have expired the average survival after initial surgery was 22 months; yet 14 lived 30 months, seven 36 months, four 4 years, five 5 years, three 7 years, and three 9 years. Were it not for the fact that a microscopic diagnosis was made in each instance, one would suspect from the sudden prolongation of life with this method of treatment in comparison to the others that an error had been made. Of this group, 70 per cent were alive at the end of 1 year following surgery. Opponents of this method of treatment may say that it is unscientific and actually stimulates growth of the cancer, the end results indubitably prove that resection has a place in treatment of prostatic carcinoma. The seemingly high operative mortality rate needs explanation. One patient died on the tenth postoperative day from sudden pulmonary hemorrhage due to unsuspected tuberculosis. One died of coronary occlusion on the operating table before 2 gm. could be resected. One death resulted from transfusion reaction; the patient also having a large bladder tumor, transitional cell carcinoma grade 3. Three patients died in 1932 and 1933 from hemorrhage and shock. The remaining 6 causes of death were: Bronchopneumonia 2, uremia 2, pulmonary thrombosis 1, pyonephrosis 1.

TABLE 7.—*Suprapubic prostatectomies*

Total number of cases 3	
Evident metastasis on admission	0
Died in hospital following surgery	1
Total available for evaluation	2 cases
Still alive	0
Died since discharge	2
Life span 8 and 26 months respectively. The longer survival also had two series of x-ray treatment.	

TABLE 8.—*Transurethral resection alone*

Total number of cases 145	
Evident metastasis on admission	31 or 21%
Died in the hospital	11
Not traced	13
Total available for study	121 cases
Alive June 1, 1946	8
Average survival	70 months
Number of those who have died	113
Average life span from first admission	22 months

Two of these patients who underwent transurethral resection as well as other therapeutic measures arrived in the hospital with a suprapubic tube (table 9). On the others cystostomy was done as an emergency procedure and was later followed by resection. The average survival in this small group is likewise relatively high.

Perineal prostatectomy was carried out in 22 cases. Six were simple prostatectomies either because the surgeon was not aware of the carcinoma in the large glands or upon exposure found extension beyond the capsule which did not permit the contemplated radical operation (table 10). Needless to say, there was no demonstrable metastasis on admission in any patient.

TABLE 9.—*Transurethral resection with other measures*

Total number of cases 12	
Evident metastasis on admission	4
X-ray treatment	4
Cystostomy	6
Cystostomy and x-ray	2
Hospital death	1
Total available for study	11 cases
Alive June 1, 1946	2
Survival since diagnosis	70 and 105 months
Died since discharge	9
Average survival after diagnosis	25.2 months

TABLE 10.—*Simple perineal prostatectomy*

Total number of cases 6	
Died in the hospital	1
Total followed up	5
Alive June 1, 1946	2
Survival after surgery	76 and 47 months
for an average of 61 months.	
Died since discharge	3
Survival average	46 months

TABLE 11.—*Radical perineal prostatectomy*

Total number of cases 16	
Not traced	1
Total available for study	15
Alive June 1, 1946	8
Average survival since surgery	52.6 months
Died since discharge	7
Average survival	35.8 months

One of the patients still alive had orchiectomy a year ago for a metastatic lesion. The 3 patients who have died surprise us with survival periods of 36, 78, and 24 months respectively, or an average of 46 months.

There was no operative death in 16 radical perineal operations (table 11). The series is small, and it means that in 400 cases only 4 per cent were considered candidates for radical extirpation, which offers the only chance of cure. Of the 7 patients who died, one committed suicide shortly upon discharge. One died

24 months after surgery of a cerebral accident. Five apparently died from carcinoma. Two of the 5 had orchiectomy and stilbestrol for extensive metastasis (table 12). Eight patients are still alive, but they are not cured. They have survived 64, 66, 56, 50, 47, 45, 31, and 62 months respectively. Three recently have had orchiectomy for metastasis. Three are receiving stilbestrol, 1 mg. daily, showing however neither local recurrence nor metastasis. They may have been cured, but only time will tell. These survivors have lived decidely longer since operation (one-half nearly 5 years) than patients treated by any other method mentioned above.

TABLE 12.—*Endocrine treatment*

Total number of cases 103	
Also had transurethral resection	72
Perineal prostatectomy	6
Metastases at start of treatment	52 or 50.5%
Stilbestrol	22
Orchiectomy	28
Both	53
Died in the hospital (without surgery)	1
Not traced	3
Total available for study	99
Alive June 1, 1946	43
Well, or minimal complaints	30
Ailing with much complaint	13
Average survival from admission to June	47.4 months
Died since discharge	56
Average survival from admission to death	18.5 months

TABLE 13.—*Endocrine therapy alone*

Total number of cases 23	
Died in hospital	1
Not traced	2
Total available for study	20
Metastasis on admission	16 or 80%
Stilbestrol	5
Orchiectomy	4
Both	14
Alive on June 1, 1946 (lived 52, 46, 45 months so far)	3
Average survival from admission to June	47.3 months
Died since admission	17
Average life span from admission to death	16.6 months

In this entire group many patients died 1 to 2 months following initiation of treatment, arriving here in extremis. Attention is drawn to the fact that all survival periods are given from the time of diagnosis on the original admission. Castration may have been resorted to later upon recognition of the metastatic lesion.

Transurethral resection was carried out in the above group to relieve the urinary obstruction There was no operative mortality, comparing the above group with those who had only a resection, we find that 86 per cent of those having transurethral operation alone were dead at the end of 36 months, whereas only 46 per cent of those having transurethral operation and endocrine therapy were dead at the end of 40 3 months. The patient's comfort and life expectancy have been appreciably improved.

Although the small group receiving endocrine therapy alone may not be representative, the result of the analysis is significant (table 13). These patients had no obstructive symptoms, but all had advanced carcinoma Eighty per cent had metastasis when first seen. This is the same type of patient who prior to 1942 was sent home without specific treatment or at best received a series of x-ray treatment He used to live an average of 8 to 10 months. (See tables 4, 5, and 6)

DISCUSSION

Comparison of the various methods of treatment is difficult since the indications for treatment were not precisely the same Thus graphical presentation purporting to show the relative survival would not be a true curve since metastases were present in 80 per cent receiving one type of treatment and only in 25 per cent with another With any form of treatment there will always emerge out of a group of patients a few who live many years It seems evident that prostatic carcinoma is extremely slow growing in isolated instances. In this type of gland the method of treatment receives unfair credit. On the other hand, we are dealing with an advanced age group subject to all the degenerative diseases and even without carcinoma, many of them would die of other lesions. But once the diagnosis of carcinoma is made, that is given as the cause of death on the death certificate

A comparatively large group of patients had no treatment at all or at least only palliation Nearly all were seen prior to 1940. These patients as a rule had no urinary obstruction; they were poor surgical risks, or they had advanced carcinoma without pain. One had a laminectomy to relieve the pressure on the spinal cord due to a metastatic lesion Another had a colostomy, the large carcinoma causing complete rectal occlusion A few refused any form of treatment, and others were discharged with an inlying urethral catheter upon digitalization here These patients survived an average of 8 months following diagnosis or 33 months from the onset of symptoms Six of the group lived over 4 years from the onset of symptoms. In the future a like series will be eliminated since the advent of estrogenic therapy.

Suprapubic cystostomy did not prolong the life of the average patient. In addition he has to contend with the apparatus and he certainly is neither comfortable nor happy

X-ray was never given with the intent to cure It has, however, improved the pain associated with metastatic lesions in about 50 per cent of the cases for varying lengths of time. This form of treatment will be relegated to a minor role in the future Estrogens and orchiectomy will be tried first.

Transurethral resection definitely prolonged the average life of the patients. We had 9 per cent survival of 5 years. Five survived 5 years, three 7 years, and three 9 years. These patients are all symptom free. We are under the impression that transurethral resection has a definite place in treatment of carcinoma. It is the treatment of choice in patients with obstruction where the lesion is too advanced for perineal enucleation.

Radical perineal prostatic resection was forever kept in mind when appraising a patient. The following criteria were demanded before the patient was subjected to the operation: 1) The gland had to be freely movable. 2) There could be no evidence of metastasis. 3) The patient had to be a fair surgical risk and have a good life expectancy. The operation probably should not be performed after the seventh decade. Only 16 patients met these requirements. We have not succeeded to effect a 5 year cure in 50 per cent, but 5 of the living have survived 64, 66, 56, 50, and 47 months respectively by June 1, 1946. Three enjoy excellent health. Eight of the 16 are alive and have survived an average of 52.6 months since surgery. How long they will remain alive awaits observing. Nevertheless this operation offers the only chance of cure. A section and biopsy of the suspicious area are always indicated. Should perineal approach be resorted to in all suspicious and questionable cases, more carcinomas undoubtedly would be detected.

The patients who received endocrine treatment do not present a homogeneous nor a closed group. The present group is unselected and has been followed like the others. It has been observed that up to 80 per cent respond to this form of treatment for varying lengths of time, some dramatically within a few days. Immediate results were more frequently noted following orchiectomy, particularly the amelioration of the pain. A few patients admitted on crutches walked out 10 days later symptom free. Estrogen therapy was not a useful supplement in cases of failure with orchiectomy. Side effects of estrogen therapy have been noted in the form of gynecomastia painful nipples, and induction of relative and complete impotence. These symptoms disappeared upon withdrawal of the drug. The observation of the last 5 years clarified for us the indication of type of treatment for the control of androgenic activity. We are using stilbestrol in all cases definitely diagnosed as having carcinoma. Orchiectomy is reserved for those patients who show objective evidence of metastasis.

Estrogenic therapy combined with transurethral resection is the operation of choice for prolongation of life and relief of pain. Early radical perineal prostatectomy is just as safe and offers a hope of cure in about 4 per cent of the patients seen.

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OBSERVATIONS IN THE USE OF INOSITOL IN ADVANCED MALIGNANCY OF THE GENITO-URINARY TRACT[1,2]

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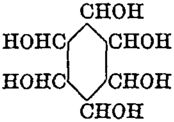
Inositol is an experimental, nutritional compound and is regarded as a member of the vitamin B complex group and has the following chemical formula:



It is found as a normal constituent in the cells of practically all plant and animal tissues. Large amounts have been found in yeast, molds and certain species of bacteria. It has also been isolated from animal tissues and body fluids such as skeletal and heart muscles, lungs, liver, brain, blood, milk, urine, eggs, etc.

A number of different forms of inositol are known. It exists in the liver in an alkali-labile combination with a large molecule, presumably a protein. A combined form exists in heart muscle and possibly other types of muscles. Some inositol occurs in the free state. In plants the majority is present as phytin, which is the calcium and magnesium salt of inositol. In the tubercle bacillus and the soybean, inositol is in combination with the phosphatide fraction as a glycoside.

It is an extremely stable compound with a slightly sweet taste, soluble in water but insoluble in absolute alcohol or ether. It can be determined in tissues and foods by means of a microbiologic assay employing a specific strain of yeast as the test organism, or by chemical methods.

Inositol was first recognized as an important factor in animal nutrition by D. W. Wooley in 1940, who isolated the substance from liver and found that it cured a disease in mice which was of dietary origin and was characterized by retarded growth and alopecia. It has also been shown to be a growth factor in the chick, in young mice and in rats. Its addition to a highly purified diet practically doubled the growth of cotton rats.

In June 1943, it was reported by Laszlo and Leuchenberger that intravenous injections of inositol were found to inhibit tumor growth in mice, the degree of inhibition depending upon the dose injected. It also acts as a lipotropic factor, preventing the development of fatty livers.

Observations by Martin, Thompson and co-workers have noticed a marked increase in the peristalsis of the stomach and small intestines in animals receiving

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 6, 1947.

[2] Inositol was furnished by the Department of Research Medicine of the Winthrop Chemical Company.

the present time he requires only an occasional dose of Demerol at bedtime. We believe inositol has had a rather favorable influence on the symptoms.

As of January 1948, 2 patients have had a succession of new papillary tumors, despite inositol on a prophylactic basis.

SUMMARY

Inositol was used in 13 patients with advanced malignancy. The cases of carcinoma of the prostate, carcinoma of the penis and seminoma of the testicle, all with metastasis, as far as we could determine from their clinical course, did not receive any beneficial results from the use of inositol. However the cases of carcinoma of the bladder were definitely influenced as manifested by the disappearance of hematuria and a reduction in size of the original tumor growth. There was 1 case of hypernephroma of the kidney which has had a symptomatic response to this drug. A number of these patients are still receiving the medication and will be brought back for periodic check-ups.

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THE DETECTION OF CANCER CELLS IN THE URINE: A CLINICAL APPRAISAL OF THE PAPANICOLAOU METHOD

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The detection of cancers of the vagina, cervix, and uterus by means of the vaginal smear method of Dr. George N. Pananicolaou has proven valuable and practical, so that other possible fields of application for the technique were considered. The method depends primarily on the exfoliation of cells and groups of cells from the tumor which can be gathered for smearing on slides. The urinary tract would seem well suited for study by the method as urine sediment is easily obtained and probably would contain exfoliated cells. Accordingly, such a study was begun with Dr. Papanicolaou. A preliminary report on the results obtained in the first 83 cases has been made and the attempt was considered promising. The study has been continued so that up to 6 months before the time of this writing 333 cases had been so investigated. While not large, the group is sufficiently great to determine approximate types and extents of possible errors and weaknesses. Furthermore, the group was selected in that not only a large percentage of patients with genito-urinary neoplasms, as well as normal patients, but also many patients with non-neoplastic urological diseases were included. Accordingly a considerable variety of cells in these urines which could theoretically cause confusion was present. The series obviously was not a cross-section of the general population nor necessarily of a general urological or cancer practice.

Early in the study it became evident that histologically benign neoplasms did not put out cells sufficiently deviated from the normal to enable Dr. Papanicolaou, who examined all specimens, to differentiate them. Thus the detection of histologically benign papillomas and inflammatory polypi of the urinary tract usually failed, though in some instances of luxuriantly growing benign tumors distinctly atypical cells were found. In this regard it should be recalled that the histological dividing line between benign papilloma and papillary carcinoma is by no means always sharp, there being papillomas with atypical cells which at the same time are not histologically actually cancer. When a malignant tumor was present in contact with the urine, abnormal cells were usually found in the first sediment smears examined but in some instances, especially the renal parenchymal and prostatic cancers, several specimens were examined before malignant cells were demonstrated. In this paper when more than one specimen from a patient was examined, the report from Dr. Papanicolaou which most indicated that cancer was present has been used in each case. Thus it may appear here that malignant tumors were easily detected, as indeed they were in most instances, but not invariably to the extent that a single specimen provided the evidence. A few cases had many specimens, and especially at the beginning, the interpretation of cells was sometimes difficult. At the same time, we should say that we have been impressed by the facility with which Dr. Papanicolaou has adapted the method to this new field. By using the report most indicative of cancer in each case, more false positive reports will be demonstrated. As false positive reports are especially undesirable, this type of tabulation is particularly useful here. It is not always possible to state positively from biopsy or clinical grounds that a given patient has a malignant tumor at the specific time the urine for study is obtained. We have, therefore, divided the cases into those with clear evidence of genito-urinary cancer at the time of the examination of the urine (on the grounds of biopsy or overwhelming clinical evidence); those with a strong suspicion of cancer but in which clinical and biopsy evidence was not conclusive (the six or more month's follow-up greatly decreased this group); and those in which there was not even a good suspicion of genito-urinary cancer nor did such suspicion appear in six or more months. Briefly then, there would be the clinically cancerous, the clinically suspicious, and the clinically non-cancerous groups to be compared with Dr. Papanicolaou's reports. His reports are made in five classes but from the clinician's viewpoint they are reduced to three: no evidence of malignant cells found in the urine, suspicious elements noted in the urine but not sufficient for a diagnosis of cancer (rather like the pathologist's common request for more or better biopsy material); and definite evidence of malignant cells found in the urine. These reports will be termed the laboratory noncancerous, the laboratory suspicious, and the laboratory cancerous. If the method were one hundred per cent perfect and a perfect tabulation were possible, the "clinical" and "laboratory" groups would be composed of exactly the same cases in each category. No perfect means is yet available to diagnose and exclude cancer. Some of the difficulties in the present tabulations have been mentioned and finally we must add that human judgment was at times necessary in the clinical classification particularly when there was no recent biopsy. Clinical data were furnished Dr. Papanicolaou only after he had made his report, except that in a few difficult cases, in which several specimens were sent for examination, a consultation was held during the study.

One hundred and ninety-eight cases were reported from the laboratory as without evidence of malignant cells in the urine sediment. One hundred and seventy-six or 88.8 per cent of these were clinically noncancerous, 8 or 4.1 per cent were clinically suspicious, and 14 or 7.1 per cent were clinically cancerous. Of the 14 clinically cancerous, 13 were biopsy proven (one a testicular cancer) and the fourteenth was a clinically advanced instance of prostatic cancer. One of the 8 clinically suspicious had previously had carcinoma of the bladder, but that disease could not be demonstrated at the time the urine specimen was obtained. From these items, it is apparent that the method as here applied will detect a large percentage of urinary tract cancer, but not all, so that this technique is of limited, though also of significant, value in excluding urinary cancer.

Fifty-three cases were reported from the laboratory as suspicious but not warranting, by the evidence in the smear, a diagnosis of malignant neoplasm. Twenty-four or 45.3 pr cent of these were clinically cancerous, 19 being biopsy proven and the remainder quite obviously so on clinical grounds. Six were clinically suspicious, and 23, clinically non-cancerous. From these figures it seems *that a suspicious report from the laboratory is significant,* and as previously noted, seems equivalent to the pathologist's request for more or better material.

Eighty-two cases were reported from the laboratory as having definite malignant cells in the smear. Seventy-one or 86.5 per cent were clinically cancerous, 63 being biopsy proven and 8 clinically obvious. Eight were clinically suspicious but not definitely with cancer: two have a distorted pyelogram, two had bladder tumors of some type but biopsy was unsatisfactory, two had hard irregular prostates but biopsy (possibly not adequate) did not reveal cancer; one had had cancer of the bladder but cystoscopy was negative when the specimen was obtained, and one had abdominal metastases from carcinoma of a kidney which had been removed. Finally there were 3 cases reported from the laboratory as cancerous, in which no cancer could be demonstrated by apparently satisfactory biopsy and which clinically were little more than suspicious. Two of these three, however, did have definite papillomas of the bladder and the other's prostate, while impressive clinically, was biopsied via the perineum without finding cancer in the paraffin section. We should mention also that in the beginning of this study one patient persistently had unusual cells in the smear which Dr. Papanicolaou thought probably malignant but subsequently these cells have been found several times in cases obviously without neoplasm. Thus the inspection of the clinically suspicious and clinically noncancerous cases in which a "laboratory cancerous" report was made reveals no absolutely clear instance of a false positive report. Also the most likely possibilities for a clear false positive report occurred in instances of a suspicious feeling prostate but with a negative biopsy. As previously pointed out, atypical areas do occur in papillomas and the dividing line from papillary cancer is not always sharp. Hence a laboratory report of malignant cells in the smear seems quite reliable though perhaps not infallible. (See table 1.) *The method is not intended to replace tissue biopsy.*

TABLE 1. *Comparison of Dr. Papanicolaou's reports with clinical findings (malignan tumors only)*

	PAPANICOLAOU'S CLASSES		
	I-II Negative	III Suspicious	IV-V Positive
Patients showing			
No malignant cells in urine total	198		
Suspicious cells only		53	
Malignant cells present total			82
Clinical evidence			
Clinically cancerous		24	
Total and per cent	14 (7 1%)	(45 3%)	71 (86 5%)
Clinically suspicious		6	
Total and per cent	8 (4 1%)		8 (9 9%)
Clinically non cancerous		23	
Total and per cent.	176 (88 8%)		3 (3 6%)

Three cases deserve special notice as bladder cancers were found because the smear report caused a more thorough search in patients being investigated for other urological diseases. In two of these the symptoms suggested prostatism, there was infected residual urine, and the prostate was enlarged. In both Dr. Papanicolaou's report of malignant cells in the urine sediment was the first indication that cancer was also present. A detailed cystoscopic search under spinal anesthesia failed to identify tumor in one of these cases but cancer inside a bladder diverticulum was found in both on suprapubic exploration. The third case was one of a patient referred for evaluation of a peculiar pyelogram which had been made for supposed calculus in the ureter. Most of our attention was directed to repeating the pyelogram with oblique views, etc. Malignant cells were consistently found in the bladder urine and once in the suspected kidney's urine. In spite of much argument pro and con it was decided best to remove the kidney which was done and no neoplasm found. Postoperatively malignant cells were still present in the bladder urine so a detailed cystoscopic search was made under spinal anesthesia. After some time a pale, small, papillary tumor was seen just behind the ureteral orifice which on biopsy proved to be a low grade papillary carcinoma. Aside from some object lesions on more systematic examinations and not concentrating entirely on one suspicious area, this case does demonstrate that a ureteral catheter can drag cancer cells from the bladder up into the kidney. After treatment of the bladder lesion, cancer cells disappeared from the urine.

As this study progressed bladder cancers appeared to provide the most suitable situation for applying the method. This is as would be suspected since exfoliation would likely be profuse and only confused by inflammatory or radiation effects. In a group of 36 patients with histologically proven benign bladder tumors, the laboratory report was: no malignant cells in 27; suspicious cells only in 8; and malignant cells found in 1. The detection of benign papillomas by the method as at present applied therefore is of little value. In 67 patients with histologically proven malignant bladder tumors at the time urine was obtained for study the laboratory reports were: malignant cells found in 49; suspicious cells found in 10; and no malignant cells found in 8. Most likely more malignant cells would have been found in this group if more urine samples had been examined, particularly as only one specimen was often sent for examination. Catheterized specimens, especially from females, usually present less confusing elements than voided ones, but the vast majority in this report were voided. The presence of malignant bladder tumors could not be absolutely ruled out by the test alone but the vast majority could be readily detected. Further practice and more specimens per patient will likely reduce the number of bladder cancers missed by this method, which is not intended to replace cystoscopy, biopsy, etc.

Some not settled points of interest, and possibilities, have come to attention during the study. The change in the character of the cells after estrogenic therapy in cases of prostatic cancer has been notable so that Dr. Papanicolaou usually reports correctly that the patient must be receiving hormone therapy. Other aspects of hormonal effects on the genito-urinary apparatus, and other tumors, might be so studied. Several times during the investigation malignant cells could be found in the urine sediment after all visible cancer had been removed.

In many instances a tumor has subsequently reappeared, thus suggesting that the method might be of prognostic and follow-up value.

CONCLUSION

Dr. Papanicolaou's technique for the detection of malignant cells in the urine sediment of patients with urinary tract cancer has been vastly better than our expectations. Falsely positive reports have been almost, though not quite, nonexistent, and even in the very rare possible instances there remains a notable doubt of the absence of cancer from the clinical evidence. A suspicious smear report from the laboratory means cancer nearly half the time, and therefore dictates more study by the usual urological means as well as by this method. A negative laboratory report decreases the possibility of urinary tract cancer being present but does not reliably rule it out. The method as now applied is of very little value in the detection of benign tumors, and is of greatest value concerning bladder cancer (but not benign papilloma). The obtaining, preserving, and preparing of specimens is inexpensive, quite simple and not time-consuming. The authors cannot reliably comment on the difficulties in the microscopic interpretation except that it would seem more than likely that any person well trained in pathological microscopy could learn the recognition of these cells and patterns without difficulty. Dr. Papanicolaou himself examined these slides and often spent much time on a single specimen. More than one specimen for examination is advisable. We would caution against clinical application until a fairly large series has been tested against the usual data, especially biopsy, by anyone just beginning. We point out also that this study is not complete and thus new problems may come to attention. Finally, it is not intended that this method should supplant or exclude recognized methods but rather that it may provide another tool for the detection and study of urinary cancer.

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EXPERIENCES WITH STAINED SMEARS OF CELLS EXFOLIATED IN THE URINE IN THE DIAGNOSIS OF CANCER IN THE GENITO-URINARY TRACT: A PRELIMINARY REPORT[1]

RICHARD CHUTE AND DAVID W. WILLIAMS

From the Urological Service of the Massachusetts General Hospital, Boston, Mass.

The recognized excellent results in the diagnosis of cancer of the uterus and cervix by the finding of exfoliated malignant cells in stained vaginal smears achieved by Papanicolaou and also by the Vincent Memorial Laboratory of the Massachusetts General Hospital using the Papanicolaou technique, followed by the publications of Papanicolaou and Marshall, and Papanicolaou, indicating that this method might be of value when applied to the urinary sediment, inspired the authors to undertake this study.

The authors hasten to acknowledge a great debt of gratitude to Ruth M. Graham, B. S. of the Vincent Memorial Laboratory of the Massachusetts General Hospital; also to Dolores Chapman, Marjorie Soule and other workers in the same laboratory. Without their help this study could not have been done, as they prepared, examined and interpreted the smears, and thus made our study possible. This is a preliminary report of a series which the authors realize was not controlled as closely and accurately as desirable, but it describes our first experiences with the technique of urinary smears.

The diagnosis of carcinoma of the urinary tract usually presents no great problem because of the modern methods of study, such as cystoscopy, biopsy and x-ray examination. However this study was undertaken to see how reliable the urine smear method might be in the diagnosis of cancer, with the thought that, if accurate, it might have use as a screening test applicable to large numbers of patients, being simpler and less expensive and less bothersome to the patient than cystoscopy, etc. Also it was hoped that it might help in the diagnosis of very early carcinoma of the prostate, in the diagnosis of certain puzzling cases of kidney disease, and in the differentiation between renal cyst and renal tumor.

The work started in June 1946, and the technique used was that described by Papanicolaou. The second urine smear done was positive and paved the way to a diagnosis of carcinoma of the renal pelvis in a case in which it had previously been partly unsuspected. When this was confirmed at operation, the authors' enthusiasm went to fever pitch. However this enthusiasm soon abated, as many subsequent smears were unsatisfactory for adequate examination, and smears from pathologically proven cases of cancer failed to show malignant cells. Despite these discouraging results 2 cases of carcinoma of the prostate and 2 cases of carcinoma of the bladder were diagnosed by smear in this series. Finally Mrs. Graham suggested a change in technique as follows. Instead of adding 10–20 cc 95 per cent alcohol to 40 cc of urine and then centrifuging, as recommended by Papanicolaou, the entire fresh urine specimen was first centrifuged in a number of test tubes, the sediments pooled and then were fixed in 95 per cent alcohol. This slight modification seemed to work much better, and incidentally saved a lot of 95 per cent alcohol. Other than that no deviation was made from Papanicolaou's technique. Three stained slides of the sediment were made for each urine. This new modification made such an improvement in the results that it was decided to discard all the first series of cases numbering 62, and the results reported in this paper are based entirely on the work since this modification.

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[1] Read at annual meeting, American Urological Association, Buffalo, N. Y., June 30, 1947.

The microscopic examination of the slides in the search for exfoliated tumor cells requires much experience, especially as the criteria are not always definite and absolute. The tumor cells are identified largely on the basis of marked variation in size and shape, dark hyperchromatic staining nuclei, giant nuclei, and absolute or relative increase in the size of the nuclei in ratio to the amount of cytoplasm. The examiner scores the slides as "positive" for malignancy or as "negative," and all slides in which the examiner is uncertain are scored as "doubtful." A "doubtful" smear calls for repeat examinations of more urine specimens until a "positive" or "negative" diagnosis can be made. The statistical scoring is based on the first slide upon which a definite "positive" or "negative" diagnosis can be made. For instance, if the first slide is reported "negative" in a proven case of carcinoma, this is scored as a mistake, even though subsequent smears may be "positive." The diagnosis in any case is not known to the examiner, until after the slide has been scored, the decision "positive," "negative" or "doubtful" being made entirely from the examination of the smear. Unfortunately in many cases, there is too little cellular sediment on which to make a diagnosis, and also if the urine is not quite fresh the cells may degenerate, and thus be useless for study. All such cases are thrown out as unsatisfactory. The first voided specimen in the morning should be used, and taken directly to the laboratory.

In accordance with our aim to obtain a practical evaluation of this method, and also in order to gain experience in the interpretation of cellular findings in urine, urines were examined from a variety of ages, sexes and diagnoses, both cancerous and non-cancerous. Most of the urines were voided specimens, but some were catheter specimens. However there was one requirement, which was insisted upon in order to have the results of any value. That was that each patient had to have a definite diagnosis, based either on actual pathological examination of tissue or on a definite clinical diagnosis. Without this, it was believed that the smear results could not be properly controlled and evaluated, and such cases were excluded from the series.

A total of 338 urine specimens from 256 different patients were examined. Many of the slides made from these urines were unsatisfactory for diagnosis either because they contained too little cellular material or because the cells had degenerated, and therefore they were discarded. Also all slide results which remained scored as "doubtful," often due to failure to obtain further urines for repeat examinations, were discarded as being of no positive determinative value. Also a good number of patients had to be eliminated from this study as unsatisfactory in helping evaluate the method, because a definite diagnosis was never established. As a result of these discards which were made in order to keep accurate control of our series, the number of urines which could be definitely scored as "positive" or "negative" were decreased to 194 coming from 168 different patients. Thus it is apparent that much effort was unproductive of definite results.

Of these 168 patients, 109 had no malignant disease. Of these 109, 96 (or 88 per cent) were correctly called negative, while 13 (12 per cent) were incorrectly diagnosed as positive. Fifty-nine patients had malignancy of the urinary tract and in 32 of these (55 per cent) the malignant disease was detected by the smear, while it was missed in 27 others (45 per cent). Thus in this series of 168 patients, 128 or 77 per cent were diagnosed correctly either positive or negative, the total error being 23 per cent. See table 1.

On reviewing the 59 malignant cases, it was found that the 29 carcinomas of the bladder comprised the largest group, 19 of which (65 per cent) were diagnosed by smear. It was interesting that most of the bladder tumors which were not diagnosed were of the small papillary type of fairly low malignancy (grade IA–IIA), and there was only 1 extensive carcinoma that was missed. A corollary to this was the fact that all but 2 of the bladder carcinomas diagnosed were of no less than grade II malignancy, and half of these were of grade III and IV malignancy. Also many of the tumors giving positive smears were of the B type, primarily infiltrating, whereas there was no B type tumor among those giving negative smears. Thus it would appear that the more malignant a bladder tumor is, the more apt it is to be discovered by urine smear.

TABLE I

59 patients with malignancy of urinary tract
  55% correctly diagnosed as "positive" by urine smear
  45% incorrectly diagnosed as "negative" by urine smear

109 patients without demonstrable malignancy in urinary tract
  88% correctly diagnosed as "negative" by urine smear
  12% incorrectly (?) diagnosed as "positive" by urine smear

Total 168 patients with and without malignancy in urinary tract
  77% (128 patients) diagnosed correctly as either "positive" or "negative" by urine smear.

When the carcinomas of the prostate are considered, it is really surprising that so many (10 out of 24 or 42 per cent) should have given positive urine smears, as one would not expect a sufficient number of the prostatic cells to get into the urethra to be of diagnostic value. The results of a small series of smears on prostatic secretions (which is to be added to and published later) has given approximately the same percentage (40 per cent) of positive smears on prostatic secretions in cases of carcinoma of the prostate. Interestingly enough, urethral catheter drainage did not prevent at least 2 cases from yielding positive smears, although it is the opinion of the authors that voided urine is more apt to contain the sought-for cells. It would seem that massaging the prostate before the pa-

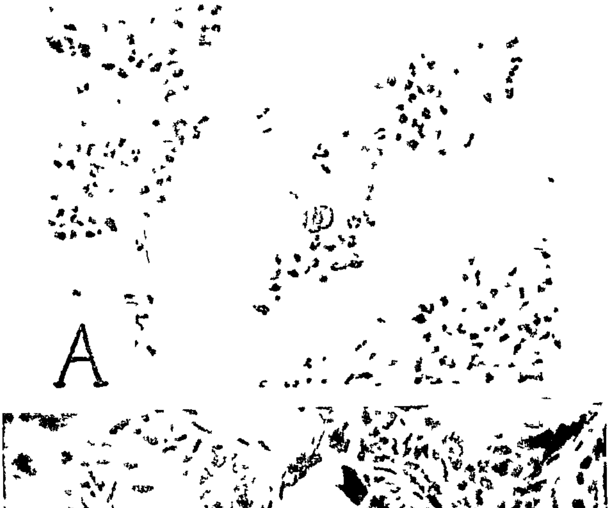

Fig. 1. Photomicrographs (× 100) of case of adenocarcinoma of prostate. Patient R. B. *A*, *Papanicolaou stain of urinary sediment, showing 3 malignant cells together in center of field.* Note size of these cells in comparison with surrounding polymorphonuclear leucocytes. *B*, Histological section from prostate, showing large number of malignant cells, grouped in form of rough oval, similar to those seen in urinary sediment. (Hematoxylin and eosin.)

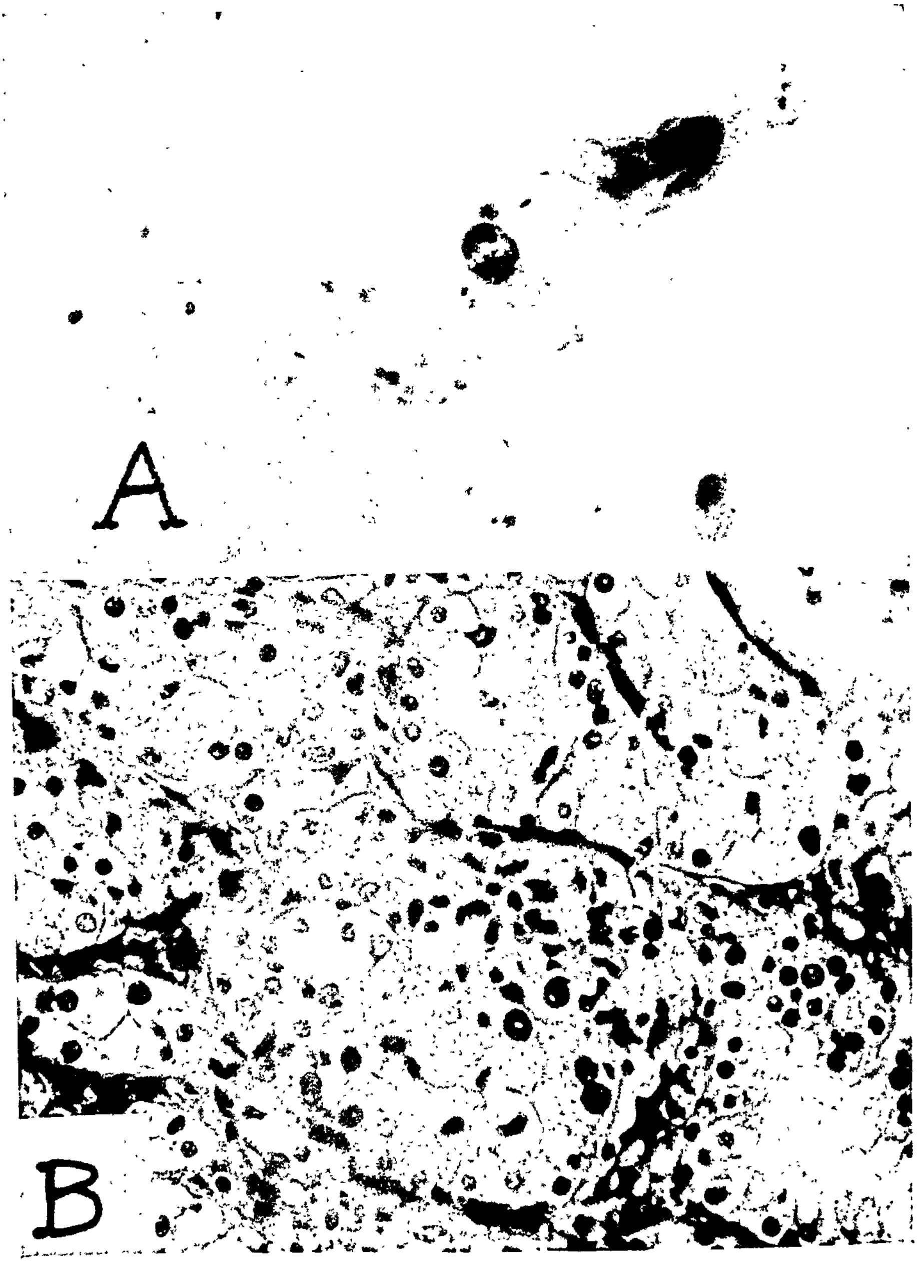

FIG. 4. Photomicrographs of case of renal cell carcinoma (hypernephroma). Patient P. S. *A*, Papanicolaou stain of urinary sediment, showing large malignant cell near center of picture. *B*, Histological section from kidney tumor, showing number of large malignant cells similar to that seen in urinary sediment. (Hematoxylin and eosin.)

tient had voided, and then having him void after the massage, should be the combination most apt to be productive of a positive smear. In half the cases diagnosed the patients were taking stilbestrol and at least 1 patient had had orchidectomy. As far as could be determined the grade of malignancy of the cancers of the prostate had no obvious relationship to whether or not they were diagnosed by smear. It is reasonable to expect that the location of the malignant tumor in relation to the bladder or urethra may be of considerable importance in this regard. In 58 per cent of the cases of prostatic malignancy the urine smear was scored as negative for malignancy.

One out of the 3 cases of renal cell carcinoma of the kidney parenchyma was diagnosed by smear. On pathological examination, this case showed extension of the tumor into the renal pelvis. One of the cases missed had no red blood cells in 2 urinalyses, and pathological examination showed no invasion of the pelvis by the tumor.

The only case of carcinoma of the renal pelvis gave a "positive" smear. One of carcinoma of the cervix, which had involved the bladder, was diagnosed, but surprisingly enough a grade II carcinoma of the female urethra was not. In this latter instance, it is not known whether the specimen was voided or catheterized, but the latter is suspected. Two out of 3 cases of benign renal cyst were diagnosed correctly as "negative," but one was called malignant in error.

It is the 12 per cent of cases incorrectly reported as positive that are most bothersome. It seems probable that a number of those patients giving repeated strongly positive smears but in whom no malignancy was discovered, will eventually be found to have carcinoma, and they are being followed closely. As for the others, it can only be said that with more experience in interpreting these slides, some of which are extremely puzzling, the results should be better in the future. It is believed by some that occasionally chronic inflammation or irritation in the urinary tract will cause the transitional epithelial cells there to somewhat resemble malignant cells. Also it has been stated that ureteritis cystica may give a somewhat similar picture. Two renal operations were carried out partly only on the basis of falsely "positive" urine smears; one showed a renal cyst, the other an essentially normal kidney. One had hematuria and both had x-ray findings suggestive of tumor so that the operations were not performed largely on the basis of the smear, but undeniably the "positive" smears were additional evidence in the wrong direction.

In some ways this first year's preliminary work with urinary smears has been disappointing in that the results of considerable time and effort had to be discarded as not well-enough controlled to be of real value to our series, and the accuracy of the results so far has not been up to that in malignancy of the uterus and cervix. Undoubtedly part of the reason for this is that, in accordance with our aim to obtain a practical evaluation of this method which might be applicable as a screening test for large numbers of people, most patients had examination of only one specimen of urine. There is no doubt that repeat examinations would result in a higher percentage of positive smears. This was shown in a number of our cases where the first specimen was "negative," "doubtful" or "unsatisfactory," while the second or occasionally the third specimen yielded a "positive" smear. This would indicate to us that this method probably is not suited to be a screening test for large numbers of people.

On the other hand, 3 cases of malignancy were first diagnosed by smear, having been previously partly unsuspected. One patient had 3 positive urine smears before carcinoma of the bladder was finally diagnosed by a second biopsy at the eighth cystoscopy. Another patient who gave positive smears of both urine and prostatic secretion had negative Silverman needle and open prostatic biopsies, and only after a perineal prostatectomy was grade III adenocarcinoma of the prostate spreading along the bladder neck diagnosed. The smear on the third patient lead to the diagnosis and subsequent removal of extensive carcinoma of the renal pelvis.

In any case in which there is particular interest, two or three smears should be done. Also, as remarked before, another specimen of urine should always be sent when the first smear is reported "doubtful." In this series, it was planned to always do that, but sometimes there were slip-ups and repeat urines were not sent when the first report was "doubtful." If this had been done in all our "doubtful" cases, the results would in all probability have been better, as a number of "positives" had the first smear reported as "doubtful," and also some cases of proven malignancy where the first slide was "doubtful", never had another slide, and therefore were discarded from the series.

See figures 1, 2, 3, and 4.

CONCLUSIONS

This is a preliminary report on our experiences with the examination of stained smears of cells exfoliated in the urine in the diagnosis of cancer in the genito-urinary tract.

In the examination of several hundred urines there was a lot of waste of effort, time and material due to smears being unsatisfactory for diagnosis. The chief reasons for unsatisfactory smears were either that the cells had degenerated because the urine was not fresh enough or that the urine contained too little cellular material to examine.

In order to have the results of value, it was insisted that patients have a definite diagnosis based either on actual microscopic examination of tissue or on a definite clinical diagnosis. If this was not possible, such patients were excluded from the series.

A total of 338 urine specimens from 256 different patients were examined, but after the discards due to the already mentioned factors of unsatisfactory slides or incomplete diagnoses or follow-ups, the number of urines which could be called definitely "positive" or "negative" was decreased to 194 from 168 different patients, and the figures are based on this fairly well-controlled group.

One hundred and nine patients had no malignancy, and 96 (88 per cent) were correctly called "negative," while 13 (12 per cent) were incorrectly diagnosed as "positive."

Fifty-nine patients had malignancy of the genito-urinary tract and in 32 of these (55 per cent) the malignant disease was detected by smear, while it was missed in 27 (45 per cent). Thus in this series of 168 patients, 128 or 77 per cent were diagnosed correctly as either "positive" or "negative."

Sixty-five per cent of 29 carcinomas of the bladder were detected by smear. Most of these were of at least grade II malignancy, and half of them grades III and IV. Practically all of the bladder tumors missed were of low grade malignancy and of the papillary type.

Forty-two per cent of 24 carcinomas of the prostate gave "positive" smears. Half of the cases diagnosed had been on stilbestrol; one had had orchiectomy. The grade of malignancy of cancers of the prostate had no apparent relationship as to whether or not they were diagnosed by smear.

A "positive" diagnosis by smear was made on one of the 3 cases of renal cell carcinoma. This case showed extension of the tumor into the renal pelvis, one of the undiagnosed ones did not. The only case of carcinoma of the renal pelvis was diagnosed by smear.

Two out of 3 cases of renal cyst were diagnosed correctly as benign, but one was falsely called malignant.

The 12 per cent of cases incorrectly reported "positive" are disturbing. However in those cases where the tests are repeatedly "positive," it seems quite probable that undiagnosed malignancy is present, and such cases are being followed closely.

Three cases of malignancy were first diagnosed by smear, having been previously partly unsuspected. One patient had 3 "positive" smears before carcinoma of the bladder was finally diagnosed at his eighth cystoscopy and second biopsy. Another patient who gave "positive" smears of both urine and prostatic secretion, had negative Silvermann needle and open prostatic biopsies and only after a perineal prostatectomy was grade III adenocarcinoma of the prostate, spreading along the bladder neck, diagnosed. The "positive" smear on the third patient led to the diagnosis and subsequent removal of extensive papillary cancer of the renal pelvis.

It has been demonstrated in this series that repeat examinations increase the probability of detection of the malignant cells. Therefore with more experience in interpreting the smears, and with slides on at least 2 urines from each patient, and repeat urines on all "doubtful" smears, the results should improve in accuracy.

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DISCUSSION

Dr. Archie L. Dean (New York, N. Y.[1]): I can best amplify the experiences so well described by Doctor Chute by reciting the results obtained from the examination of stained smears of the urine from 333 patients seen in Doctor Stevens' Service of the New York Hospital and the Department of Urology of the Memorial Hospital. Since these tests represent Papanicolaou's fundamental work on the diagnosis of tumors of the genito-urinary organs by recognition of desquamated tumor cells in the urine, many specimens from patients with diseases of the genito-urinary organs other than tumors were submitted. All of the examinations in this series were made by Papanicolaou and to obtain the diagnostic value of a 9 months period of observation of a small group of patients with originally unproved clinical diagnoses no tests are reported which were performed later than September 1946.[2]

After studying smears from a group of patients with bladder papillomas (table 1) it became evident that cells exfoliated from microscopically benign tumors showed no recognizable differences from normal cells. Difficulty also may be experienced in recognizing as cancerous cells from tumors of a low grade of malignancy. These considerations, therefore, show the test undependable in detecting the great majority of bladder tumors. It was noted that more than one examination may be necessary before cancer cells can be found in cases of clinically demonstrable growths of the renal parenchyma and prostate. Therefore, lacking strong clinical evidence these diagnoses might have been missed. As would be expected, the smear test was found unsuitable for detecting tumors of the testis or kidney after nephrectomy even when metastases were present.

Negative smear tests agreed with clinical diagnoses in about 90 per cent of patients examined (table 2).

Table 3 compares equivocal smear tests with the clinical conditions present. The laboratory report "suspicious of cancer" means that the microscopic test was uncertain and that additional urine specimens and further clinical data are requested. It may be seen that in this group the clinical diagnoses were divided almost equally between benign and malignant conditions. While not a definite microscopic diagnosis, suspicious findings warrant further clinical investigation in unproved cases.

In table 4 Papanicolaou showed the greatest accuracy and he should be commended for reporting few, if any, false positive tests.

Of all cancers of the genito-urinary organs those of the bladder appear most suitable for accurate diagnosis from smears. Table 5 indicates that cystoscopy with removal of a portion of the growth is more accurate.

The smear test was of great value in 2 patients with benign prostatic hyperplasia. Cancer cells were reported but clinical examinations failed to find tumors because they were within diverticula.

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[1] From the Department of Urology, Memorial Hospital, New York, N. Y.

[2] I am indebted to Drs. Carl J. Schmidlapp and Victor F. Marshall for the statistical studies on which this discussion is based.

In conclusion I would say that the smear test when performed by Papanicolaou, a man with more than 20 years experience, intensely interested in the success of the method, and who will spend hours, if necessary, examining a single specimen, has corroborative value in diagnosing the most malignant tumors of the urinary tract. When performed under other conditions the value of the test is questionable

TABLE 1. *Examination of smears from 36 patients with bladder papillomas*

	Cases
No malignant cells	27
Suspicious cells	8
Cancer cells	1

TABLE 2 *Negative smear examinations*

	Cases	
No microscopic evidence of cancer	198	
No clinical evidence of cancer	176	89%
Clinically suspicious of cancer*	8	4%
Clinically proved cancer	14	7%

* The patients classified as "clinically suspicious" had clinical evidence of tumors without microscopic verification such as distorted pyelograms, indurated prostates or proved bladder cancers at a previous time

TABLE 3 *Equivocal microscopic findings*

	Cases
Microscopically suspicious of cancer	53
Clinically cancer	24
Clinically suspicious	6
Clinically non cancerous	23

TABLE 4 *Microscopically positive for cancer*

	Cases
Microscopically cancer	82
Clinically cancer	71
Clinically suspicious	8
No clinically demonstrable cancer	3
(Papilloma of bladder (2), indurated prostate with negative perineal biopsy)	

TABLE 5 *Smear test of 67 histologically proved bladder cancers*

	Cases
Cancer cells found	49
Suspicious of cancer	10
No cancer cells found	8

DR JAMES B CROSS (Buffalo, N Y.): I was very much interested in Dr. Chute's paper, because we have been doing some work along the same line at the Deaconess Hospital.

The pathological work was done by Dr Tannhauser, pathologist at the

Deaconess Hospital. He has done considerable work on cancer of the lung from sputum specimens. These cases are all of renal tumor. They were taken by cystoscopy.

There were 20 specimens examined. Three of the 5 cases of proven malignancy had a positive diagnosis made. Two of these cases are renal cell carcinoma, one papillary carcinoma, one renal calculus, and one more case received the interpretation of "suspicious cells found, please repeat." The patient was operated upon before a second specimen was obtained. This proved to be carcinoma.

I have asked Dr. Tannhauser to demonstrate the slides.

Dr. Tannhauser (Buffalo, N. Y.): (Slide) This is from a papillary carcinoma of the pelvis, and you see here the tumor cells with the large nuclei.

The next slide is from the same patient. This specimen was obtained at a second examination. You see exactly the same tumor formation and the diagnosis was confirmed by operation.

(Slide) This is from a so-called clear cell carcinoma. You see the nuclei are so much smaller than in the papillary carcinoma of the pelvis. You see here the clear cell.

(Slide) This is also from a clear cell carcinoma. Can you see the relatively small nuclei?

(Slide) This is a suspicious case which remained unproved. Again the same cell architecture and the same large nuclei.

The technique we used is somewhat different than that used by Drs. Chute and Papanicolaou. All of these slides were made from paraffin embeddings of the sediment obtained at catheterization. We often embed a very minute amount of cells in plasma which afterwards are coagulated by adding a little calcium chloride. We obtained coagulum embedded routinely, paraffin-like in the other specimens.

We have never made a diagnosis from single cells. We have always made diagnosis from clumps or masses of cells, and this is, I think, a much more reliable method.

In the last 2 years we made 20 examinations of specimens obtained cystoscopically. Fifteen of them were completely negative and were proved negative in the clinical follow-up; whereas one was found negative which, as Dr. Cross said, was proven carcinomatous at operation.

Dr. D. M. Davis (Philadelphia, Pa.): I wish to say just a few words in regard to the diagnosis of carcinoma of the prostate by means of Papanicolaou's stain. As you recall, a paper on this subject was presented by Drs. Herbert and Lubin of the Jefferson Hospital, at the meeting of the Mid-Atlantic Section of this society last spring in Washington, and has been published in the *Journal of Urology* (March 1947). At the time of this publication, they had studied very carefully over 200 cases.

It would seem to me that in this work it would be very important to distinguish between the detection of cancer of the prostate and the detection of cancer of the urinary tract proper; that is to say, the bladder, ureter and kidney.

There are two reasons for this. In the first place, the cell picture of prostatic cancer is quite different from those arising from the transitional epithelium of the urinary tract. Secondly, these cells are within the substance of the prostate and it is extremely unlikely that an adequate supply of them would be present in an ordinary specimen of voided urine to make a reliable diagnosis.

Certainly, with careful study of expressed prostatic secretion, the percentage of correct diagnoses is much higher than that reported by Dr. Chute.

Further, we find that the percentage of correct diagnoses goes higher, and the percentage of uncertainty goes lower, as the experience of the pathologist with this method increases.

It is, as Dr. Chute has brought forward, and also Dr. Cross, necessary in many instances to repeat the examination. This is particularly true in small, hard prostates from which it may, in certain instances, be impossible even after several trials to express any secretion whatever. In such cases, of course, the method does not work.

In regard to the danger of doing prostatic massage in case of cancer, I agree of course that there is such danger, and one should not perform prostatic massage on a case obviously of cancer, but this test is not to be used in cases that are obviously cancerous, and its primary importance, its tremendous and thrilling importance, is that it may be the means by which we can detect prostatic carcinoma early enough to cure it by radical operation, and that is the way we have to cure it if we are going to cure any cases at all.

Now, if the case is doubtful, I submit, gentlemen, that the danger of performing prostatic massage on such a case is less than the danger of letting the cancer go unrecognized.

Dr. Richard Chute (Boston, Mass.): I think Dr. Dean and I are in fundamental agreement, that, so far as urines go, this is an interesting adjunct to our diagnostic armamentarium, but as yet it is not of primary importance. Possibly at some future time it may assume that importance. When you realize that, even in the hands of Dr. Papanicolaou or of our workers at the Massachusetts General who have done thousands of vaginal smears, mistakes are made sometimes, think what the average laboratory worker will do.

I am also indebted to Drs. Cross and Tannhauser, and I was interested in Dr. Tannhauser's slides and in his method. However, it is much more of an undertaking to prepare slides by his technique than by the Papanicolaou technique, which is a practical disadvantage of his method.

When it comes to Dr. Davis's remarks, I am in complete agreement with him, but the prostatic secretion in carcinoma of the prostate is a separate situation from the urines about which I am speaking today. I had thought of bringing our rather small series of prostatic secretions into this report, but I decided I would just stick to the urines and put the secretions in carcinoma of the prostate in a separate paper. Frankly, we were perfectly amazed that we should have got 42 per cent of positives in the urine from carcinomas of the prostate, because one wouldn't expect many prostatic cells to be obtained in voided urine.

Also I would agree with Dr. Davis that the risk of spreading early carcinoma of the prostate by a massage or two is certainly well worth running, if one can thereby diagnose them early enough to have a good chance of being able to cure them by an early, radical prostatectomy.

Our thought, when we started this work, was that this might be used possibly as a screening test for hundreds of people. In other words, if a patient came into a big clinic, one of the screening tests he might have would be a cytological examination of the urine. The way things look now, a good many cases of cancer in the urinary tract would be missed, if only one specimen of urine were examined routinely in a screening test.

URETHRAL STRICTURE: A PATHOLOGICAL STUDY[1]

DONALD E. BEARD AND WILLIAM E. GOODYEAR

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The pathology of urethral stricture has not been as carefully studied as have other urological diseases in recent years. This has in some measure been due to the prevalent opinion that the disease is decreasing since better methods for treatment of gonorrhea have been available for more than 10 years. That the pathology of the disease is little understood is exemplified by the fact that there have been few if any advances in its management for more than two decades. Accordingly, a study of the pathology of urethral stricture would appear worthy of report.

The material upon which this report is based consists of 211 consecutive cases of urethral stricture treated at this clinic during the course of a year. All questionable cases were discarded as were so-called "large caliber" strictures, and only those cases having a caliber of 12 French units (4 mm.) or less were used. Each patient was evaluated by history, physical examinaton, various urethral instruments, urethrography, and pathological study of specimens removed at operation and autopsy.

Much of the information regarding the gross pathology was obtained by urethrography which was performed in every case. The examination was made by injecting 30 to 40 cc. of an iodized oil into the urethra and making an oblique x-ray film while injecting the last few cubic centimeters of the medium. From this examination the exact location, number, length, and caliber of strictures can be accurately measured.

The material which was available for microscopic examination was obtained from operative specimens in which the strictured portion of the urethra was removed. A few cases were found incidentally at autopsy when patients had died of other causes.

CAUSE

Comprising the 211 cases were 192 Negro and 19 white males. It has been long a casual observation that the Negro race has a greater tendency to develop certain diseases which have fibrous tissue as the basic pathology. In this region there is definitely a higher incidence of gonorrhea in the Negro. The ratio of cases is approximately 8 to 1.

The ages of the patients varied from 16 to 93 years with the majority being between 30 and 50 years. Only 10 per cent occurred before the age of 30 years which is explained by the prolonged interval which elapses after gonorrhea before the stricture is of such severity as to cause the patient to seek medical attention. See table 1.

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[1] This study was made possible by a grant from G. D. Searle & Co., Chicago, Ill., makers of Iodochlorol, the contrast medium employed.

Pathologically, an urethral stricture is not formed by scar tissue in the wall of the urethra alone but by the contraction of fibrous tissue which replaces the corpus spongiosum for its entire thickness. The scar tissue is the result of inflammation or thrombophlebitis of the corpus spongiosum. In some cases of gonorrhea, the inflammation of the urethra extends directly into the corpus and in others follows rupture of a periurethral gland. In traumatic stricture, the scar tissue likewise forms in the corpus spongiosum and is due to injury of that structure. In some cases of periurethral abscess and urinary extravasation, the thrombophlebitis and consequently the stricture extend for the entire length of the corpus. Urethral stricture then results from 3 major causes: gonorrhea, trauma, and periurethral inflammation.

TABLE 1. *Age*

Years	*Cases*
Less than 20	2
20–30	20
30–40	66
40–50	53
50–60	39
More than 60	31

TABLE 2. *Cause*

Gonorrhea		190
Years since gonorrhea		
Shortest—18 months		
Less than 5 years	11	
5–10 years	24	
10–15 years	26	
15–20 years	38	
20–25 years	38	
25–30 years	28	
More than 30 years	35	
Trauma		11
Instruments	6	
Medications	1	
Wounds	3	
Stone	1	
Periurethral phlegmon		4
Unknown		6

Ninety per cent were caused by gonorrhea, 5 per cent by trauma, 2 per cent by periurethral inflammation, and 3 per cent gave no history which would suggest the etiology of the disease. Ninety-two per cent of the whole group were then either the direct or secondary result of gonorrhea. See table 2.

Analysis of these cases indicates that the urethral stricture does not immediately follow gonorrhea but that many years elapse before the lesion is of such severity as to cause the patient to consult a physician. Only 5 per cent had symptoms in 5 years or less, while 66 per cent had gonorrhea 15 years or more before they first presented themselves to the clinic for treatment. Thirty-four per cent had had gonorrhea more than once. The length of time between gonorrhea and stricture varied from 18 months to 70 years but averaged 21.5 years.

Chemotherapy had been used in only 10 per cent for gonorrhea. Most of those were in the early days of the sulfonamides and were treated with sulfanilamide. Only 2 cases had been treated with penicillin.

In 11 cases stricture developed as a result of trauma, of which 6 were caused by injury to the anterior urethra by transurethral resection of the prostate. In these, an indurated area was observed along the urethra a few days after the resection, and within a few months there was a well-defined stricture of the bulbous urethra. Such a stricture is caused by rupture of the anterior urethra with localized inflammation in the corpus spongiosum. This type of stricture is common but is decreasing since the use of perineal urethrotomy for insertion of the instrument.

Two cases resulted from rupture of the urethra by a displaced bone fragment in severe fracture of the pelvis. Another resulted from the impaction of a large calculus in the anterior urethra while another was due to a straddle injury.

The retrograde injection of antiseptic solutions has been considered a common cause. This is substantiated by the fact that forceful injection into a diseased urethra frequently causes extravasation into the corpus spongiosum or veins of the penis. In 1 case it was believed that there was an actual chemical burn of the urethra by the injection of a caustic substance.

In some cases of periurethral abscess and urinary extravasation, there occurs severe and extensive thrombophlebitis of the corpus spongiosum for its entire length beginning 1 to 1½ cm. distal to the sphincter. A stricture results which is very dense, and the prognosis of such a case is cheerless. Ten cases (5 per cent) were of this type.

As a rule, stricture which develops after trauma or periurethral inflammation develops in a far shorter time than those which result from gonorrhea. The former are well formed within a few months while the latter require an average of 21.5 years to produce symptoms.

GROSS PATHOLOGY

An urethral stricture is composed of dense fibrous tissue which involves the corpus spongiosum and that portion of Buck's fascia which surrounds the latter structure. There are all variations of number, length and caliber. Cut in cross section, the restricted caliber of the urethra will be observed to traverse the mass of scar tissue near the innermost edge leaving approximately 3 times as much tissue on the external aspect. The contracted fibrous tissue is so tightly adherent to surrounding tissues that sharp dissection is needed to separate it from the corpora cavernosa. The tissue is pale, white or gray, and is irregular and nodular to palpation. Near each extremity of the fibrous mass the stricture gradually fades into normal corpus spongiosum with strands of fibrous tissue extending almost a centimeter into otherwise normal corpus spongiosum.

Calculus was a major complication occurring in 7 per cent of cases with the urethra being the most frequent site. These cases were all associated with infection by an organism having the ability to split urea.

Periurethral abscess and urinary extravasation are frequent complications of stricture. The former occurred in 17 per cent of cases, while the latter was present in 6 per cent. Both are a direct result of stricture and both diseases produce additional stricture usually quite long and frequently for the entire length of the urethra.

TABLE 7. *Complications*

Periurethral abscess		35
Urinary extravasation		12
Calculi		
Urethral	6	
Vesical	4	
Renal	1	
Prostatic	3	
Upper tract disease		
Hydronephrosis		3
Pyelonephritis		5
Cystitis		3
Urethral adnexal disease		
Inflammation of periurethral glands		2
Inflammation of Cowper's gland		3
Prostatitis		51
Epididymitis		24
Inflammation of glands of Littré		1
Acute retention		124
Urethral complications		
False passage		5
Sinus		11
Fistulae		10
Hyperplasia of prostate		10
Carcinoma of prostate		1
Uremia		4
Elephantiasis		1
Deaths		2

Due to the chronic obstruction caused by stricture, urinary infection occurs in some cases associated with such conditions as hydronephrosis, hydroureter, and trabeculation or diverticulum of the bladder. Such stasis and infection were noted in 12 per cent of the group.

Acute urinary retention is an inevitable complication in neglected cases, occurring in 124.

Incidental findings were 10 cases of hyperplasia and 1 case of carcinoma of the prostate. Five cases had false passage in the anterior urethra as a result of inexperienced and unskilled sounding. Twenty-one patients had sinuses and fistulas which were the result of untreated periurethral abscess. See table 7.

SUMMARY AND CONCLUSIONS

A study of urethral stricture has been made and the results reported.

The disease is caused by gonorrhea principally, but it is also the result of trauma, periurethral inflammation, and urinary extravasation.

Strictures which result from gonorrheal inflammation require an average of 21.5 years to produce symptoms, while those resulting from trauma or periurethral inflammation are well formed within a few months.

The incidence is much higher in the Negro race due to the prevalence of gonorrhea and its complications.

Approximately 57 per cent of strictures occur between the ages of 30 and 50. Only 10 per cent occur below the age of 30.

A stricture results from localized thrombophlebitis of the corpus spongiosum by direct extension of gonorrhea, extravasation of antiseptic solution by retrograde injection, trauma to corpus spongiosum, or by generalized thrombophlebitis due to periurethral abscess or phlegmon.

Pathologically, a stricture is composed of fibrous tissue involving the outer coats of the urethra, corpus spongiosum, and Buck's fascia. The scarring in these latter structures which surrounds the urethra is the fundamental disease in stricture.

Eleven per cent of strictures are multiple.

The disease occurs in that part of the urethra surrounded by the corpus spongiosum. It most frequently occurs in the bulbous portion but is found in all parts except the proximal 1 cm. of the anterior urethra.

Multiplicity, length, and caliber can be accurately measured by urethrography.

The urological adage that prostatic hyperplasia does not occur in combination with stricture is not substantiated.

Complications which are common and are frequently severe are tabulated.

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PEYRONIE'S DISEASE AND ITS TREATMENT WITH RADIUM[1]

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A disease which neither threatens life nor disturbs any vital function would not seem to demand serious therapeutic effort or detailed study. However, Peyronie's disease, although occurring mainly in men past the procreative age, often precludes sexual intercourse and leads to much mental distress. We have encountered 2 cases in which a fibrous plaque developed after successful irradiation for cancer of the rectum. The patients were much more worried and upset about the Peyronie's disease than they had been about the malignant lesion. Although, even if all therapeutic efforts fail, we regard Peyronie's disease as a self-limiting process, every possible effort should be made to cure the individual sufferer, if only to relieve his mental anguish.

Cabot has called Peyronie's disease one of the more common rare diseases of the penis. Since its original description by Peyronie in 1743 it has been described under a variety of names: fibrous plaque of the penis, fibrous cavernositis, chronic cavernositis, fibrous sclerosis and plastic induration of the penis. The tunics of the corpora caverosa or the intercavernous septum or both are involved in induration which may result in formation of a plaque, nodule, cord or band, readily palpable and superficial, although not attached to the overlying skin. The corpus spongiosum and urethra are not involved. On erection the presence of this plaque or band causes an abnormal bending of the penis, usually without pain, although pain may be present. This bending becomes extreme and eventually may prevent sexual intercourse altogether. Plaques have been excised for microscopic study. They exhibit bundles of collagen fibers with fibroblasts between them, a few blood vessels and not many elastic fibrils; in other words, they seem to resemble a keloid. Eventually, in long-standing untreated plaques, calcium and bone may be formed.

The etiology of fibrous plaques is unknown. A variety of chronic conditions have been cited as causative factors, but no positive proof has been forthcoming. Many urologists believe the condition is due to trauma, even though a history of trauma rarely is elicited; the belief probably is justified because of the resemblance of the lesion to keloids on microscopic examination.

Treatment has been varied and not too successful, as can be guessed because many agents are used. Johnson listed as therapeutic measures topical applications of iodine, mercury, camphor, iodoform and such drugs; internal use of iodides and arsenical drugs; injection of fibrolysin and use of electrolysis, faradic current, ultraviolet rays, short wave diathermy, excision, roentgen therapy and radium treatment.

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[1] Read before annual meeting, American Therapeutic Society, Atlantic City, N. J., June 6 and 7, 1947.

The lesion occurs in patients of any adult age, but the majority of patients are more than 50 years of age. It is found in patients of all walks of life. The diagnosis readily is made by considering the history, the symptoms and the characteristic physical findings. Formerly, it was considered a rare disease; in 1928 Polkey found 549 cases in the literature and added another. By 1940 Burford found that 40 more cases had been reported and added 40 of his own, a total of 630.

In 1939, thirty-four cases in which radium was used for treatment at the Mayo Clinic during 3 preceding years were reported. Of the 31 patients traced, 48.3 per cent were unimproved by the treatment, but the remainder had good or fair results. We have continued to treat this disease with radium since then in increasing numbers of cases. Many inquiries from other physicians and their interest in the problem have prompted us to review our experience with treatment of the condition with radium at the clinic from 1938 to 1943, inclusive.

TREATMENT

Admittedly, therapeutic efforts have yielded poor results. Polkey in 1928 summed up results of many types of treatment in 419 cases reported in the literature; only 76 patients were cured and 39 received some benefit (altogether less than a third of the cases) from any type of treatment.

However, Dreyer in 1914 gave a hint regarding effective treatment. In 1911 he saw a patient who had been rendered impotent for the past 9 months by a fibrous plaque. Dreyer stated he used heavily filtered radium just as the pioneers Wickham and Degrais had used successfully in treating keloids in 50 cases. He achieved a successful result; a year later his patient returned for treatment of a newly contracted syphilitic infection.

Physicians favor varied types of treatment. Cabot mentioned roentgen treatment or excision, as does Polkey. Johnson preferred surgical excision, but stated that recurrences are common. Corbus favored use of diathermy. Burford, Soiland and others believed that radium therapy achieved the best results.

Technique.—At the Mayo Clinic, our own preference in the treatment of this disease has been radium therapy. We have used heavily filtered radium, at a distance from the skin, over the entire shaft of the penis. To gain extension of the organ, the ends of a loop of adhesive tape are fastened to the sides of the penis; a rubber band through the center of the loop is attached to the leg just above the knee with adhesive tape, thus exerting traction. A lead plate is placed over the scrotum, as protection for the scrotum and as a support for the balsa wood blocks carrying the radium tubes. On a flap of transparent cellophane the upper margin of which is taped to the lower part of the abdomen are placed the 3 wooden blocks (each block has a base measuring 3 by 3 cm.) and each of the blocks is surmounted by a 50 mg. radium tube filtered with 1 mm. platinum. The blocks are 1 inch (2.5 cm.) in height and cover the full length of the extended penis. To the undersurface of the cellophane flap wooden blocks are taped, one on either side of the penis, as a support. The radium is left in place for 12 hours. The patient lies flat on his back; the head of the bed is elevated so he can read and keep awake during the treatment. When it is necessary to use a urinal, the patient can undo the rubber band around the loop of adhesive tape, raise the cellophane flap, void and replace the apparatus himself. The supporting wooden blocks on the under surface of the flap, one on either side of the penis, serve as guides in replacement. The dose, three 50 mg. tubes at 1 inch distance, spaced as described, for 12 hours is suberythema.

The main features of treatment are: a) by extending the penis by traction, the whole shaft is treated adequately and b) by placing radium at a distance, injury to the normal tissues can be avoided. Neither erythema nor distressing edema has occurred in any case.

Treatments are spaced 3 months apart. If no apparent benefit followed treatment, we usually stopped our efforts after the third application. Sometimes a patient was helped sufficiently by only one or two applications, so that no more treatment was needed.

TABLE 1. *Results of treatment**

RESULT	CASES	AGE	DURATION OF SYMPTOMS	TREATMENTS PER PATIENT
		years	*months*	
Excellent	14	53	17.1	1.4
Good	28	51.1	12.6	1.7
Fair	20	52	16	2.0
Poor	50	54.5	13.4	1.7

* Average figures are given.

Results.—During the 6 year period from 1938 to 1943, inclusive, 141 patients were treated with radium at the Mayo Clinic for fibrous plaque. This was an average of approximately 24 patients a year. The 2 youngest patients were 27 years old and the 2 oldest, 70 years old. The average age was 53.2 years.

One treatment only was given to 86 patients. Six patients had four treatments each. The average number of treatments per patient was 1.5.

Information concerning results of treatment was obtained by re-examination of patients or by letters from patients or from their physicians elsewhere. We were able to determine results in 112, or 79.4 per cent of the total. Our study is based on findings in these 112 cases.

We judged the results rather critically and demanded evidence of decided improvement before classifying a result as good. We found a poor result (no improvement discernible whatever) in 50 cases or 44.6 per cent. A fair result (some definite benefit) was obtained in 20 cases or 17.8 per cent. A good result was noted in 28 cases or 25 per cent and an excellent result or cure in 14 cases or 12.5 per cent.

We thought that perhaps the age of the patient, the duration of symptoms before treatment was instituted or the number of treatments might be important factors in the result of treatment. The study of 31 traced patients reported by

Olds and one of us in 1939 indicated that the patients not benefited by treatment had had the disease much longer before treatment was started and also had had fewer treatments. However, in this study of 112 traced patients, there seems to be no essential difference in results of treatment because of the patient's age, duration of symptoms or number of treatments given (table 1).

SUMMARY

Fibrous plaque of the penis disturbs no vital function and is not a serious condition; however, the disease tends to cause severe mental distress and every effort should be made to cure the condition. The disease occurs usually in middle-aged patients. It appears to be a self-limiting process. Although formerly this was considered an extremely rare disease, many more cases are being reported in recent years.

The etiology is not known. Microscopic examination of excised fibrous plaques presents a picture resembling that of keloids elsewhere in the body. Hence, trauma due to previous infections, passage of sounds or some other factor may well be the cause.

Although present methods of treatment are unsatisfactory, radium therapy given by the technique employed in treating keloids appears to be worth while. More than half the patients treated should receive definite benefit. Radium treatment of 141 patients over a 6 year period is described; 44.6 per cent of those traced were not benefited but the remainder were helped. The age of the patient, duration of symptoms before treatment and number of treatments given did not seem to be factors definitely influencing the result.

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SCLEROSING LIPOGRANULOMA OF TESTICULAR ADNEXAE

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It is seldom that one encounters a large scrotal tumor in this country. Recently such a tumor was removed by one of us (N. B. P.) which weighed over 2 pounds. Even more surprising was the microscopic appearance of the tumor, which proved to be one of the benign, although exceedingly rare, lipogranulomas of the testicular adnexae. Apparently this is the second published report of such a tumor.

CASE REPORT

J. O. B. was a single 37 year old white male of French extraction, who was first seen on February 6, 1947, because of a gradual painless enlargement of the right side of the scrotum which caused him inconvenience in walking, sitting, and lying in bed. An interesting fact was his statement of having won a bet 10 days previously from several friends by placing his enlarged scrotum on a chair and hitting it a hard blow with a hammer without flinching.

Past history, family history, and social history were essentially negative. He had been overseas about 1½ years in the China-Burma-India theater. The scrotal swelling had begun about a year after discharge from the Army.

Examination was essentially negative except for a very large swelling of the scrotum with fixation of the skin overlying the entire right testicle. The mass in the scrotum was diffuse and apparently extended into the left side. The superficial veins on the right side of the scrotum were dilated. The penis was diffusely enlarged and edematous with an irreducible phimosis. A hard mass could be felt in the distal end of the penile urethra, and a right inguinal gland was palpable.

The patient was admitted to Memorial Hospital on February 25, 1947. A Friedman test was reported negative. Under spinal anesthesia an incision was made over the right external inguinal ring and carried down to the cord, which was isolated, clamped, and severed. The proximal end was swabbed with phenol and alcohol and ligated. Two small inguinal glands were removed for section. The dissection was carried down into the scrotum, but there was no line of cleavage. The tumor appeared to originate from the testicle and had invaded an area of scrotum about 4 cm. by 4 cm., so that it was impossible to shell out the right testicle. Further exploration revealed that the tumor also had invaded along the bulbous urethra, perineum, and rectum. It had extended into the left scrotum and completely encircled what seemed to be a normal testicle. Since a frozen section diagnosis of a malignant tumor was made by the hospital pathologist, the left testicle also had to be sacrificed in order to remove the tumor *in toto*. The left spermatic cord was ligated at the external inguinal ring. A No. 20 Foley catheter was inserted into the bladder in order to delineate the urethra. With much difficulty the growth was dissected off the urethra and the rectum. Unfortunately, there was extension into the rectal wall, but it was deemed inadvisable to resect the rectum or any part of it. A plastic closure was done with the remaining scrotum, and the defect in the base of the penis was closed with stainless steel wire. A circumcision was done to relieve the phimosis.

The patient made an uneventful recovery. Healing was complete on May 26, 1947. He was last seen on September 3, 1947, at which time there was no evidence of recurrence in the incision, urethra, prostate, or rectum. His climacteric symptoms were controlled adequately by 10 mg. of oral testosterone daily.

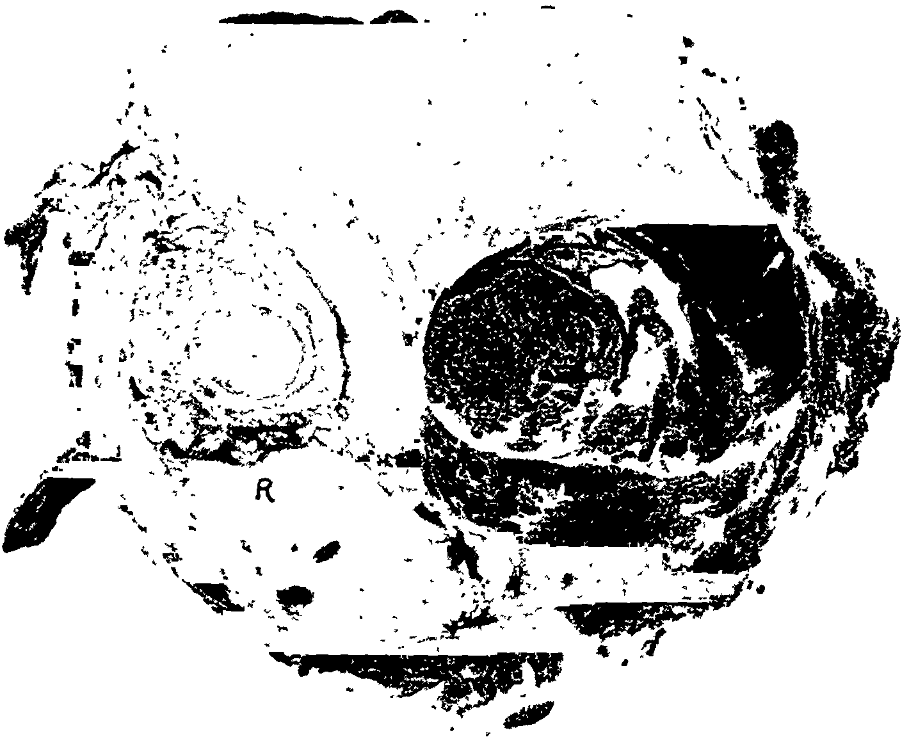

FIG. 1. Cut surface of enlarged scrotum, showing thick band of tumor tissue which has completely destroyed right epididymis and partially destroyed right testis. Early involvement of left epididymis.

Grossly the scrotal sac and contents measured 14 by 13 by 11 cm. and weighed 950 gm. They were partially covered by thickened, edematous skin. At the base of the scrotum the severed spermatic cords were enlarged and indurated, the right measuring 3.2 cm. in diameter, the left 1.5 cm. in diameter. On section there was a 2 cm. to 4½ cm. thick layer of firm, rubbery, yellowish gray tissue studded with small cystic spaces which completely encircled both testes. The right testis was compressed and atrophic, measuring 1.8 cm. in diameter. The right epididymis could not be identified as such, being completely incorporated in the tumor mass. The left testis measured 3½ cm. in diameter. Its lower pole was firmly adherent to the tumor. The left epididymis could still be identified grossly, although it too was partially replaced by tumor tissue.

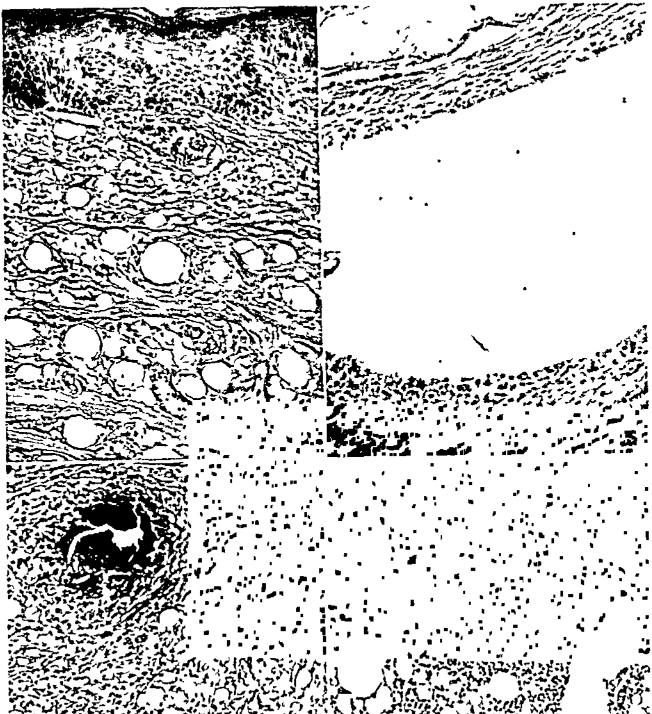

Fig. 2. (Upper left), vacuolated and gland-like spaces extend up to epidermis of scrotal skin but do not invade it. (Upper right), one of larger gland-like spaces lined by several layers of fat-filled, foreign-body type giant cells. (Lower left and right), typical microscopic appearance of "lipogranuloma." (Lower left), showing dark staining necrotic area. (Lower right), showing a more cellular granuloma (Neg. No. 101237, Army Institute of Pathology).

Sections of the tumor showed many gland-like spaces, the larger ones of which were lined by elongated or vacuolated giant cells. Some of the smaller spaces were lined by prominent epithelial cells resembling the lining cells of the adenomatoid tumor. The smallest spaces were lined by flattened, elongated spindle-shaped cells with scanty cytoplasm. Scharlach R stains showed the majority of these gland-like spaces and vacuolated cells to be filled with fat. Scattered throughout the tumor were bundles of smooth muscle fibers, collagenous tissue and small granulomas. The latter consisted of a small central area of necrosis in which amorphous masses of dark brown pigment could occasionally be seen. These necrotic areas were surrounded by foam cells, foreign-body giant cells, lymphocytes, and eosinophiles. The vacuolated cells of the tumor extended up to the epidermis of the scrotum but did not invade it.

This growth was diagnosed as a benign adenomatoid tumor of the testicular tunics by the Department of Pathology of Baylor University College of Medicine. However, the Tumor Registry of the Army Institute of Pathology sent back the following report: "The spaces within the mass of tissue certainly do simulate what is seen in certain of the adenomatoid tumors. It is, however, felt that the process is akin to what has been called here sclerosing lipogranuloma. There are a few identical cases in the files, and their nature is a mystery. In one patient the subcutaneous tissue of the entire scrotum and penis became progressively involved."

In going through the literature, the only published reference to this type of tumor which we were able to find is in the *Atlas of Genito-Urinary Pathology.* In their short introductory discussion, Friedman and Ash state: "The lipoid granuloma of the testicular adnexae is a troublesome lesion, because it may simulate a tumor clinically and tuberculoid granuloma histologically. The fat lobules which are situated along the course of the spermatic cord may undergo necrosis, especially after trauma, and a granuloma ensues. Enough cholesterol may be set free in a degenerating hematoma to provoke a similar reaction."

According to Hinman and Gibson the fat lobules along the spermatic cord may grow down along the epididymis and testis. It is highly probable that this tumor did originate in such expanding fat lobules, in which case the granulomatous reactions can be satisfactorily explained on the basis of traumatic fat necrosis. On the other hand, some of the glandular areas of the tumor are indistinquishable histologically from the so-called adenomatoid tumors of the genital tract. However, Golden and Ash did not find any fat in their 15 reported cases. If this absence of fat is accepted as characteristic of adenomatoid tumors, then our case is automatically excluded, and we are dealing with a relatively rare tumor. If not, then the lipogranulomas of the genital tract may prove to be a type or variation of the adenomatoid tumor.

SUMMARY

A large scrotal tumor of 15 months' duration which weighed over 2 pounds is reported. It was classified as a sclerosing lipogranuloma of the testicular adnexae and is the second published report of such a tumor.

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GENITAL SELF-MUTILATONS BY MENTAL PATIENTS[1]

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Self-inflicted, intentional mutilations and/or injuries of the genital organs by mental patients are not infrequently seen by the physicians in psychiatric hospitals and occasionally in private practice. Such mutilations may present at times a vexing problem for both the medical and attending personnel of the institution and require constant vigilance on their part to prevent and detect their occurrence. These injuries, their motivations and methods vary widely in accordance with the underlying mental states of the patients and constitute only one of the symptom-complexes of the disease. The histories as given by the patients themselves may seem bizarre, vague, silly or humorous, but they are always unreliable, while often it is impossible to obtain from them any coherent or plausible account of the act. As a rule these injuries are discovered accidentally, often long after their occurrence, either by another patient, the attendant or the nurse, who may have noticed blood stains or other evidences on the patient's bed clothes or about his person and brought this fact to the attention of the medical officer.

In the light of present-day sexology such mutilations are regarded as manifestations of a phenomenon called autoalgolagnia, which is derived from the Greek word "algos", meaning pain and "lagnia", meaning delight. It embraces the two concepts, sadism and masochism, or, according to the old Freudian terminology, that of pain-pleasure. The basis of this form of sexual aberration is characterized by pain inflicted, endured or only imagined, which serves as a source of sexual excitement or gratification. Freud and his desciples maintain that the urge towards the mastery over, and infliction of pain belongs to the normal sexual instinct of man. They postulate two periods in the development of this instinct, namely, autoeroticism and heteroeroticism. The first period, they assert, can continue for an indefinite time and may lead to persistence of infantile sexuality as manifested by continued indulgence in masturbation, exhibitionism, narcissism, voluntary retention of feces and urine by the children, and other deviations from normal, including the phenomenon of autoalgolagnia.

It may be of interest to mention in this connection that among some primitive peoples genital self-mutilation is widely practiced as a ritual or magico-religious rite, or as therapeutic measure in the effort to remove bad blood or evil humors from the body in case of illness. We may also refer to the practice of "subincision" among the Australian aborigines. It is their custom to incise the urethra from below the external meatus to the scrotum. Hugh C. Brown of Sydney, who amassed data in this field, states that he never saw any urethral strictures among them, and he is tempted to conclude that this is due to the fact that the doctors were scarce and the catheters were unknown.

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[1] Read before the Chicago Urological Society, March 27, 1947.

CASE REPORTS

The following cases were seen by us recently at the State Hospitals for mental diseases.

Case 1. E. F., a white male aged 52, was admitted to the Acute Ward of Manteno State Hospital on January 25, 1944. Mental classification of the patient was "dementia praecox, hebephrenic type." He was transferred from the cottage for the tuberculous patients with a note from the medical officer in charge, saying, "... he was found by an attendant, with a string tied around the penis, causing swelling of the organ and extensive tissue destruction." Upon admission to the surgical pavilion the patient appeared very weak and debilitated and acutely ill. Mentally he was confused, incoherent and disoriented, and had an associated amnesia, being unable to recall the act nor the reason for it.

General physical examination showed that the patient was in advanced stage of pulmonary tuberculosis. Inspection of external genitalia revealed a grossly swollen distorted and discolored penis in the middle of which there was a deep crease encircling the organ, with a black string buried in it, with only the ends protruding. On cutting this string it was noted that it had almost completely bisected the organ through Buck's fascia, the corpora and the roof of the urethra, leaving the distal fragment attached to the stump of the penis by the skin and the sheath of corpora cavernosa. The stump of the penis was swollen and discolored, measuring at its greatest diameter about 5 cm., while the distal fragment was pale and felt leathery and clammy to touch. The proximal urethra was somewhat retracted and there was a fistula measuring 0.3 by 0.4 cm. The external meatus could not be seen, being covered by an edematous and phimotic prepuce, which overhung it and the distal portion of the penis.

Because of frank contamination and necrosis of the tissues, it was deemed unwise to attempt any surgical repair at that time. The wound was thoroughly scrubbed with soap and generously lavaged with saline solution. Loose gauze was wrapped around the penis and kept moist with hydrogene peroxide solution. Sulfathiozole was given orally and 1500 units of antitetanic serum administered. A rubber catheter was inserted into the bladder through the proximal urethral fistula and left in situ.

Laboratory examination of the blood showed marked secondary anemia, and moderate leukocytosis. Urinalysis showed 2 plus albumin, no reduction and microscopically many pus cells and some motile bacilli. The culture of the urine revealed Escherichia coli and that of the traumatized tissues, E. coli and Staphylococcus albus. The blood Kahn was negative, the sedimentation rate, 36. Rectal examination showed an essentially normal prostate gland. Intravenous urography: no uropathy.

On January 29, four days later, under local analgesia, a suprapubic cystotomy was done and the bladder closed to a No. 28 Malecot tube. At the same time a dorsal slit was made and a small Foley catheter was passed through the external meatus into the bladder and sewed into place. Then the cut ends of the urethra were approximated over the catheter with interrupted sutures of No. 000 plain catgut and the tunica albuginea was sutured with interrupted stitches of No. 00 chromic catgut. A heavy frosting of sulfanilamide powder was applied.

The postoperative course was uneventful. He showed a mild febrile reaction which abated under the usual treatment and free use of parenteral fluids. The urethral catheter was removed on the third postoperative day and the suprapubic tube on the eighth. A small penile fistula persisted for about a month, then completely closed, leaving a soft scar and smooth skin. The patient voided at this time full stream through the external meatus. An endoscopic examination showed a small linear scar on the roof of the penile urethra over the site of recent laceration, for which dilatations were given. His recovery unhappily was followed by rapid physical and mental decline and he expired on April 7, 1944, about 3 months later. The autopsy revealed advanced pulmonary tuberculosis, severe myocardial damage and chronic pyelonephritis. Dissection of the penis showed recent fibrous scar in the roof of the urethra.

Comment. Rupture of the penile urethra occurs very seldom in civilian practice. A search of the literature and texts of urology and traumatic surgery reveals only rare reference to this type of injury. Frank Kidd states that of 14,000 cases admitted annually to London Hospital there were only 4 of ruptured urethra. Rupture of the urethra is generally regarded as the most serious of all injuries of the genito-urinary tract, not for the reason of the immediate mortality but because of subsequent ill health. "I know of no case", says Kidd, "where the urethra has been completely torn across, in which the patient was restored to perfect health." A study of the literature dealing with complete laceration of the urethra reveals the difference of opinion as to what should be done to the urethra. Every experienced urologist is agreed that as soon as possible the urine should be diverted as its escape will produce dense scarring of the surrounding tissue. Suprapubic drainage is generally accepted as being desirable. There is no agreement, however, as to the use of a catheter in the urethra for fear of subsequent stricture formaton. But as some stricturing is almost inevitable in most cases, the objection to the indwelling catheter, seems to us, loses most of its validity.

Immediate or delayed repair is also controversial. It should be decided in every case by the general physical condition of the patient and the state of local trauma. While the immediate repair is the theoretical ideal, the delay might be dictated by the presence of primary or secondary shock; but at all times such a delay should be minimal. "It is safer", says Hugh Young, "almost in every case, to go in at once and carry out an anastomosis".

In our case an amputation of the distal fragment of the penis was at first considered to assure the ability of sexual contact by means of the remaining stump, which usually retains the power of erection. It is a known fact that even though the penis may be lost almost up to the penoscrotal juncture, on erection it may extend sufficiently far to allow successful intercourse and satisfactory ejaculation. In my (L. M. B.) Army service and since, I had on occasions observed several such amputees who had lost a part of the penis as a result of an injury or following plastic operation for malignancy and, as a rule, they all professed satisfactory sexual ability. I have treated since a few of them for gonorrheal urethritis.

Case 2. W. H. G., a white male aged 19, was admitted to Manteno State Hospital on July 6, 1945. His mental classification was "dementia praecox, catatonic type." On May 19, six weeks previously, he had amputated with a safety razor blade his scrotum and its contents. Little of direct history was available in this case. It was obtained from father, a Baptist minister. The mother of the patient before her marriage was confined to a mental institution for a period of 18 months, the diagnosis was unknown. During his childhood the patient had had 3 attacks of chorea. He was always considered a precocious and queer child and had exhibited early preoccupations with sex. At an early age he came in conflict with the law because of some sexual derelictions and later was penalized for having committed numerous immoral acts with children. Subsequently the court came to the conclusion that he was a dangerous sexual offender and recommended castration. At this time, presumably as a result of the psychosexual conflict, he constantly engaged in overt acts of compulsion, thus evincing the splitting of personality. Later, under stress of overpowering sense of guilt, arising from uncontrollable and ever-increasing sexual urge, he had developed what psychoanalysts refer to as "the castration complex." This caused the patient to find some means to atone for his guilt through pain and had influenced profoundly the entire psyche. He repeatedly threatened and attempted to castrate himself, which in spite of his father's admonitions, and constant watching on the part of his family, he had finally accomplished on June 15, 1945. He was taken by his father to the Cook County Hospital where he was seen in a state of deep shock and was given first aid. Surgical repair was done the following day. The wound healed per primam within 3 weeks. Then he was transferred to the County Psychopathic Hospital and later to Manteno State Hospital. Physical examination at the latter institution revealed total absence of the scrotum and all its contents and a heavy perineal scar. Otherwise his general physical and laboratory examinations including serology were essentially negative. Mentally the patient presented the clinical picture of advanced catatonic psychosis. His stay at Manteno State Hospital was short as his mental and physical deterioration became rapidly progressive. He refused his food and had to be tube-fed. He threatened and attempted to gouge his eyes, etc. and he finally expired of exhaustion on July 25, 1945, three weeks after admission to the hospital and about 3 months after self castration. While at this hospital, owing to the general condition of the patient, no attempt was made to place him on substitution therapy with the male sex hormone and no relevant data obtained on an interesting and still a controversial question regarding the effect of castration in the adult male.

Case 3. R. M., a white male aged 24, was admitted to the acute ward of Manteno State Hospital on June 15, 1945. His mental classification was "dementia praecox, catatonic type." He was transferred from his cottage with a note from the medical officer that ". . . the patient lacerated his scrotum and amputated the left testicle with a buckle from his overalls." The amputated gonad and the buckle were found by the attendant in the patient's bed and were forwarded with him to the examining room, wrapped in toilet paper, as Exhibit A, and marked "one meatball." The exact time of, and the reason for the accident could not be obtained from the patient, nor anyone else. Upon admission to the hospital, there were evidences of shock. There was marked pallor, rapid and weak pulse, blood pressure of 68/40, etc., but as it is usual in such mental patients, he did not evince any pain or distress.

Local examination showed that the left half of the scrotum was completely avulsed from the body and that the left testicle, epididymis and major part of the spermatic cord were missing. The remaining stump of the cord had retracted almost to the external ring and there was some arterial oozing present.

While under pentothal sodium hypnosis the patient admitted that the reason for his self-semi-castration was fear of the shock-treatment which he was getting at that time.

Under intravenous anaesthesia immediate surgical repair was done. The wound was thoroughly scrubbed with green soap and freely lavaged with saline solution, then heavily dusted with sulfanilamide powder. 1500 units of antitetanic serum was administered. The stump of the spermatic cord was ligated with a No. 1 chromic catgut and the scrotum was closed with a mattress suture taken through all the layers. A small drain was inserted in the dependant part of the wound. The postoperative course was uneventful. The wound closed after about 3 weeks, leaving a normal appearing but retracted scrotum.

Case 4. L. C., a white male aged 48, mental classification, "psychosis with organic brain disease", was admitted to the hospital ward of Kankakee State Hospital on August 29, 1945 because of avulsion of left half of the scrotum.

The patient was wholly disoriented and no history was obtained from him or anyone else regarding the how, when and why of the accident.

On examination he did not appear acutely ill, nor in any pain or discomfort, though the usual institutional pallor and debility were in evidence.

His general physical examination was otherwise non-contributory. Local examination showed that the left half of the scrotum was almost completely avulsed from the body, except for a small attachment posteriorly. The left testicle was bare and hung free on the spermatic cord. It appeared swollen and edematous. The tunica vaginalis was partly torn away and necrotic while the tunica albuginea was apparently intact. The opposite testicle was not involved.

As the wound was frankly contaminated no attempt at surgical repair was done. The parts were shaved and vigorously scrubbed with green soap and lavaged with saline solution. Debridement with removal of all necrotic tissue was done. Tetanus antitoxin and sulfa powder locally and tablets orally were given. Daily sitz baths in potassium permanganate and in between soaks with sterile gauze saturated with normal saline solution were applied to the wound and held in place by a suspensory bandage.

By the seventh day the testicle was partly covered with rich granulations while a healthy edge of regenerated epithelium grew circumferentially from the remaining scrotal tissue.

By the twenty-eighth day the scrotum appeared healed save for a small area about one-half an inch in diameter which persisted for another 2 weeks before becoming completely epithelialized.

Re-examination 1 year later showed a normal appearing scrotum and no secondary atrophy of the testis.

Case 5. P. D., a white male aged 28, classified as "dementia praecox, hebephrenic type," was admitted to the acute ward of Manteno State Hospital on December 21, 1944 because of dysuria, urgency and frequency of urination. The patient was very uncooperative and combative and no history could be obtained from him as to his present dilemma.

His general examination was non-contributory. Local examination showed a swollen and red penis and mucopurulent urethral discharge. On the dorsum of the penis, at about midway of the shaft, a wire pin was protruding. Palpation disclosed a small safety pin in the urethra with the open end pointing distally.

Microscopic examination of the urethral smear showed pus cells but no organisms present.

The protruding end of the pin was grasped with an artery forceps and pulled outward until the head was reached where resistance was encountered. The pin was then so manipulated that it was reversed with the head pointing distally. The protruding end of the pin was then cut with a wire-cutter and the pin was removed with a small forceps through the external meatus.

Hot compresses were applied to the penis. The small fistula gave no trouble and promptly healed.

Nonspecific urethritis cleared under mercury oxycyanide irrigations.

On June 11, 1945, six months later, the patient was readmitted to the surgical ward with profuse urethral bleeding. He admitted introducing various foreign objects into the urethra, though an examination at that time had failed to disclose the presence of any foreign body in the urethra or bladder.

Comment. Here we have a case of onanistic manipulations performed in the manner more common to the female. It usually reveals concealed homosexuality. Also it may be due to abnormal erotic impulse as a result of insanity or intoxication.

It is obvious that surgical removal of a foreign body from the urethra will not cure him of unconscious homosexual tendencies whose roots lie in psychopathic constitution.

SUMMARY

Cases of self-mutilations and injuries of the genital organs by mental patients are presented. An attempt is made to interpret these acts in the light of modern sexology as manifestations of either congenital or acquired masochism which may be the end result or a concomittant of various psychic degenerations.

It may be stated that the practice of sexual self-mutilation constitutes merely one of the symptom-complexes of specific type of psychosis of the individual, or in terms of Freudian psychiatry it is one of the characteristics of persistance of infantile sexuality patterns.

In the treatment of mutilating wounds of the external genital organs conservative approach is always indicated. Owing to the abundance of blood supply these tissues often exhibit remarkable healing power. Even when the organ has been completely severed, in fact only attached by skin, there has been sufficient blood supply to allow anastomosis of the proximal and distal portions of the lacerated organ.

Injuries of the testes should be especially treated with great conservatism.

Only when the blood supply has been completely severed and there are evidences of necrosis should castration be carried out. Even a small portion should be preserved, if possible, to prevent making the patient a eunuch.

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A PERSISTENT CLOACA IN A FIVE YEAR OLD BOY[1]

WILLIAM J. BAKER AND J. LESTER WILKEY

From the Department of Urology of Cook County Hospital, Chicago

J. R. A., a male aged 5 years, was admitted to the Pediatric Medical Department of Cook County Hospital on June 20, 1946. His mother had brought him to the hospital because he voided all urine by way of the bowels and she was worried about the small size of his penis.

The child was born at home. The attending physician had informed the mother of the very small penis and of urination by way of the anus. The mother was told that the boy could be operated upon at puberty to correct all of his abnormalities.

This child had what was thought to be attacks of pneumonia when he was 24 and 26 months old. The first attack lasted 2 days and the second attack lasted 3 days. These episodes could have been attacks of pyelonephritis. An examination and a chest film, about 6 months later, disclosed "heart trouble." The mother had noted a rapid pulse and that the boy became tired very easily. There had never been any dyspnea, orthopnea, cyanosis or ankle edema.

This boy had received intramuscular injections of pituitary substance twice a week for 4 weeks, when he was 3 years old, to help enlarge his penis. These injections seemed to make the patient irritable and nervous. A survey indicated a cardiac disturbance and the injections were stopped. There was no change in the size of the penis.

There was no history of congenital anomalies in any other member of the family.

The child was of small stature, pale and shy. His weight was 34 pounds. The blood pressure was 98 mm. of Hg systolic and 70 mm. of Hg diastolic. He did not appear ill.

The facial expression was that of a boy. The 4 front teeth were represented by pegs. The tonsils were enlarged and inflamed. The lungs showed no abnormal changes.

The apical heart beat was very noticeable and diffuse. It was most noticeable at the base of the sternum but was also seen at the left of the midclavicular line. The heart border was enlarged to the left. There was a loud, blowing, systolic murmur throughout the heart field and a slight diastolic murmur.

There was a dimpling in the sacral region above the anus and a small irritated area of the skin just below this dimple.

The rectal examination, with a gloved finger, disclosed nothing of significance. The patient had one to two bowel movements a day. All bowel movements were liquid.

The penis was very rudimentary and appeared more like a clitoris than a penis (fig. 1). The testes were of normal size and consistence for a boy 5 years old.

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[1] Read at annual meeting, American Association of Genito-Urinary Surgeons, Absecon, N. J., June 5, 1947.

The scrotum appeared normal except for a groove which extended down the center of the scrotum almost to the anus. The mother stated that a small amount of mucus would appear on the end of the rudimentary penis 2 to 3 times a year. There was no visible external urethral meatus or palpable urethra.

The Wassermann and Kahn tests of the blood were negative for syphilis. Red and white blood cell counts and hemoglobin determination were all within normal limits.

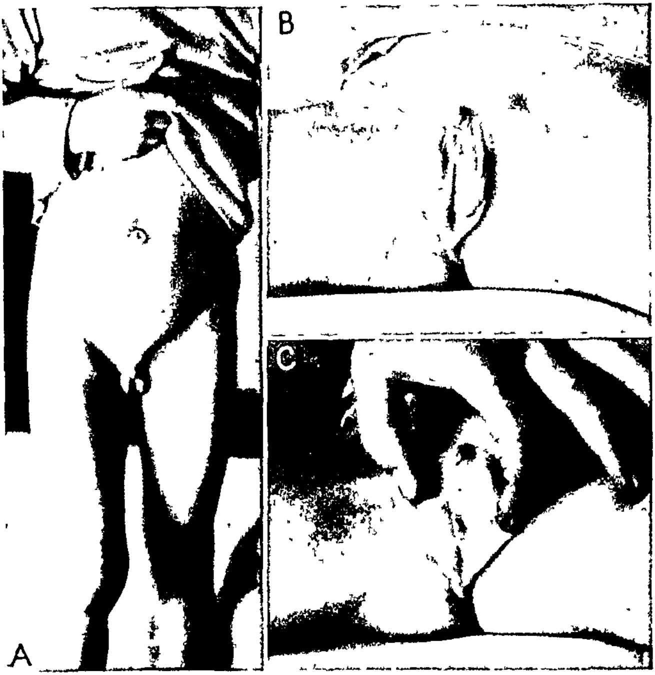

FIG. 1

X-ray study of the chest revealed the cardio-thoracic ratio to be markedly increased. The heart had an abnormal contour in that the left heart border was straight. The vascular markings were increased and radiated in all directions from both hila. The costo-phrenic angles and infraclavicular areas were clear. These findings were compatible with organic heart disease and pulmonary congestion.

The electrocardiographic tracings were definitely abnormal. The auricular

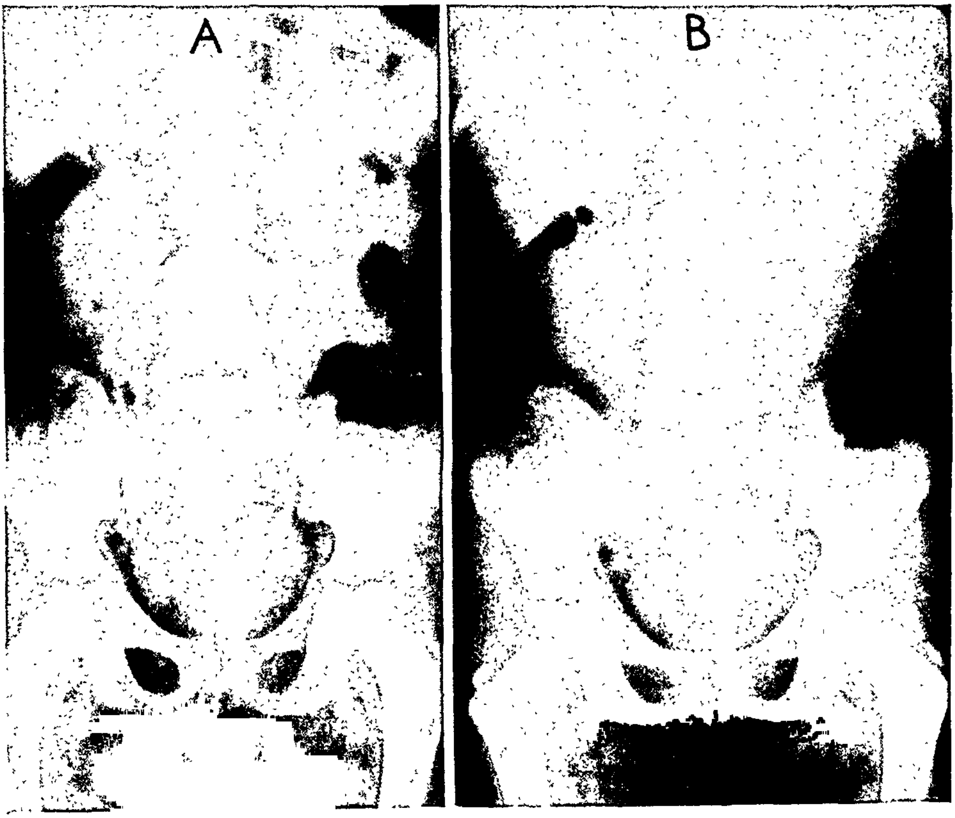

FIG. 2

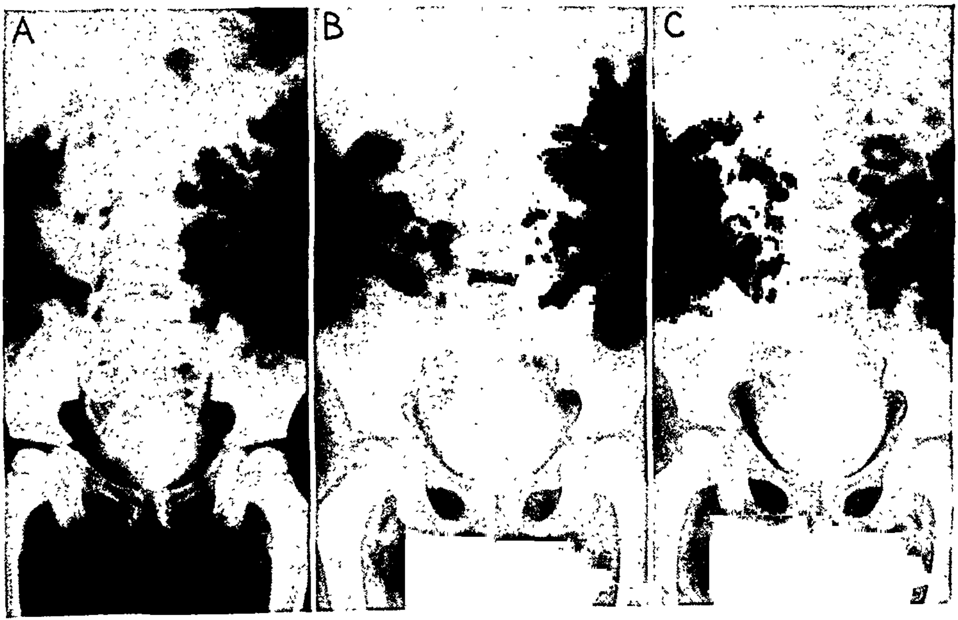

FIG. 3

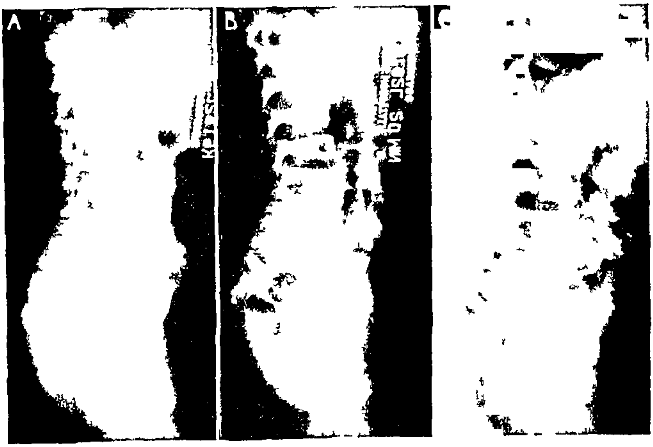

Fig. 4

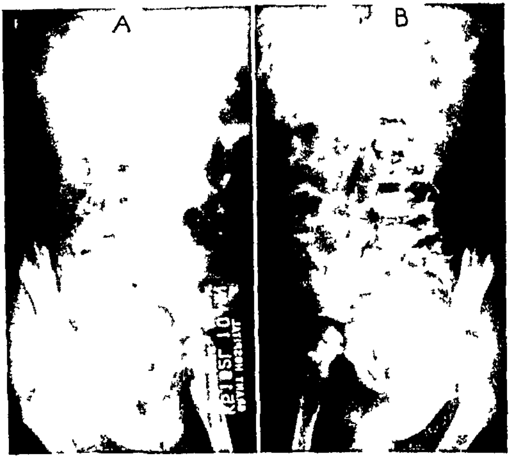

Fig. 5

rate was 96. The tracing showed a sinus rhythm. The P-R interval was 0.12. The Q R S interval was 0.06. The Q R-S was diphasic in Leads I and II and down in Lead III. A deep S_1 and S_2 were present. P_1 was small. P_3 was inverted. T_4 was upright This curve is sometimes seen with congenital heart lesions. Repeated electrocardiographic tracings revealed the above changes with right axis deviation. There was also T_1 inversion to suggest myocardial involvement.

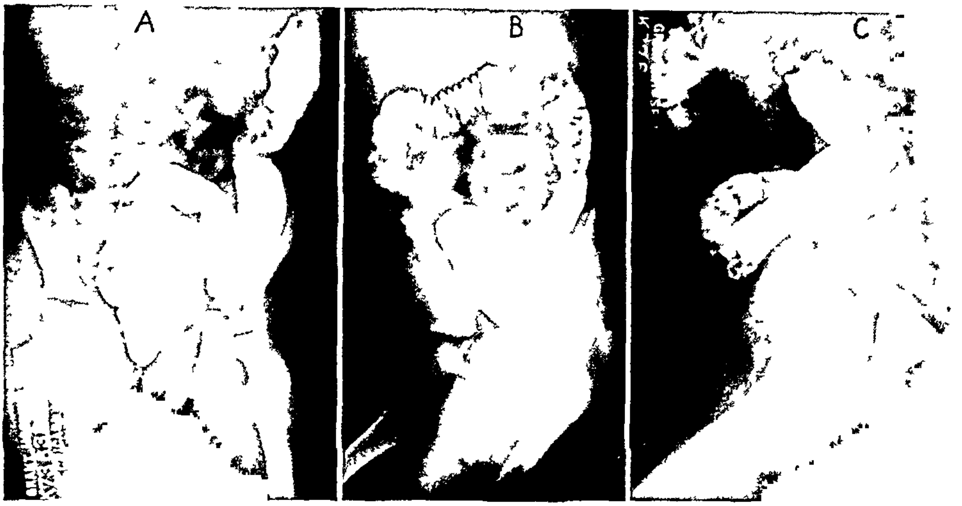

Fig. 6

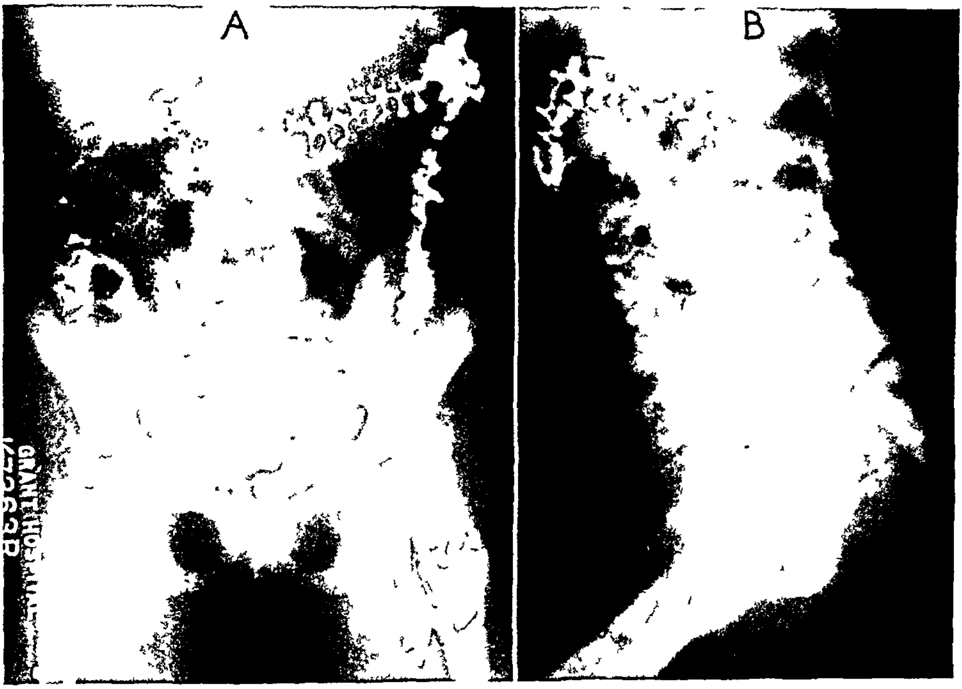

Fig 7

Plain x-ray study of the urinary tract showed renal shadows which seemed to be normal in size, shape and position. There was a pelvic shadow which could be interpreted as a full urinary bladder (fig. 2, *A*). Intravenous urograms suggested normal bilateral kidney function on the five minute film. The bladder

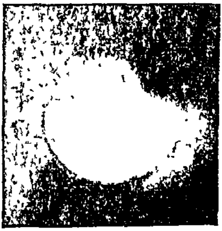

FIG. 8

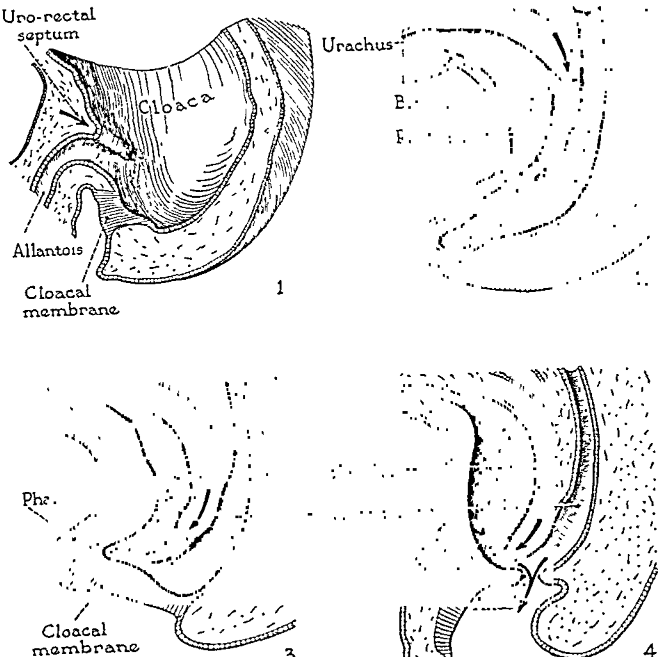

FIG. 9

was seen to be filled with dye. Attention is directed to the double density in the mid-portion of the bladder on each film (fig. 2, *B*). This double density could represent dye outside of the bladder and possibly in the rectum. These findings were very evident in the 10, 20 and 40 minute films (fig. 3). The 10, 20 and 40 minute lateral views revealed nothing of importance (fig. 4). The 10 and 40 minute oblique exposures were not significant (fig. 5).

A barium enema revealed a normal recto-sigmoid area in the anteroposterior, oblique and lateral views (fig. 6). There were no unusual traces of barium in the anteroposterior and lateral views of the rectosigmoid area after evacuation (fig. 7).

A proctoscopic examination revealed a rosette of mucosa on the ventral wall of the rectum just inside the anal sphincter. This was interpreted as a stoma or connection between the bladder and the rectum. It was decided not to pass a catheter through this rosette. Such a procedure would possibly infect the urinary tract. Figure 8 shows a picture of this area which was taken through a proctoscope.

EMBRYOLOGY

Figure 9, *1* shows the dilated caudal segment of the bowel, the cloaca; the allantois empties into this structure. Figure 9, *1* also shows the cloacal membrane which is a thin wall of ectoderm and entoderm. In a 6 week embryo, the urorectal septum, a frontal fold, passes downward to meet the cloacal membrane and separates the cloaca into a dorsal rectal and a ventral urogenital segment, from the dorsal surface of which the ureter stalks and wolffian ducts leave. The upper portion of this anterior or ventral segment becomes the bladder; the inferior portion becomes the posterior urethra in the male and the entire urethra in the female. See figure 9, *2* and *3*. It is believed that in our patient, the urorectal septum never completely joined the cloacal membrane, thereby establishing a connection between the bladder and the rectum. Thus, a persistent cloaca is present (fig. 9, *4*).

We have no evidence of a urethra in this boy. The urethra is usually derived from 1) the lower narrowed portion of the vesico-urethral anlagen above the wolffian duct opening which forms the urethra down to and including the verumontanum and utricle and 2) the urogenital sinus which begins at the openings of the wolffian and müllerian ducts and extends to the cloacal or urogenital membrane which separates the sinus from the cloacal fossa outside.

The ureters, as shown in the foregoing urograms, apparently empty into the usual location of the bladder.

LITERATURE

A search of the literature does not reveal any instance exactly similar to this patient. Campbell reports the autopsy findings in a 3 year old girl whose bladder was exstrophic and who had a rectovaginal fistula. The right ureter opened directly into the rectum and the left ureter ended blindly in the tissues on the side of the bladder. Campbell also reports that he operated on a 6 weeks old male whose right ureter was an impervious cord; there was anal atresia, urethrorectal fistula, a dilated rectum, a left pyonephrosis and a dilated left ureter which opened into the lower rectum.

Walker reports the autopsy on a 12 day old female in whom there was persistence of the cloaca. He termed the condition "ectopia of the cloaca".

Burns describes the autopsy of a 4 hour old infant with exstrophy of the urinary bladder and a persistent cloaca

Kilfoy operated on a new born child to correct an imperforate anus and found the distal sigmoid greatly dilated, and it communicated with the urinary bladder through a hard fibrous duct A colostomy was done and the child died 4 days later.

Major reported the autopsy findings of a 1 hour old male who had an imperforate anus and no urethra, there was a wide cloaca into which the rectum and both ureters emptied

Pennock and Stark operated on 2 male children, 5 years and 18 months old, because they passed fecal matter through the urethra after imperforate anus had been opened at birth In both instances there was a defect in the floor of the bulbous urethra, which defect was closed successfully in both patients by surgery.

Lowsley has reported successful operations on two girls who had a cloaca

Wharton has emphasized congenital malformations associated with agenesis of the ovarian follicular epithelium

We wish to express our thanks to Dr Leslie B Arey of the Department of Anatomy of Northwestern Medical School and his artist, Miss Lucille Cassell, for their anatomical and embryological ideas and drawings

SUMMARY

An instance of persistent cloaca and absence of the urethra in a 5 year old boy is reported There is also evidence of a congenital heart lesion

Since this child enjoys good health in spite of the persistent cloaca and since it is doubtful whether surgery would improve that which nature has already done, it was decided not to use any operative interference in an effort to correct his defects It was also recognized that he would never procreate

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THE UROFLOMETER: AN AID TO THE STUDY OF THE LOWER URINARY TRACT

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The observation that the size and force of the urinary stream are diminished in certain urologic conditions dates back well over one hundred years. Howship in 1816 mentions, in writing of stricture, that "the diameter of the stream must of necessity be lessened," and that "the stream of urine is smaller than it ought to be." In writing of benign hypertrophy of the prostate gland, he speaks of "the impediment in passing water." Brodie in 1849 adds, in discussing neurogenic bladder, that "the urine is expelled at short intervals and in small quantity at a time."

Little has been added to these general observations of the urinary stream until Ballenger in 1932 suggested that by measuring periodically the maximum distance from his feet a man with a full bladder could eject his urine, one might follow the effect of an enlarging prostate more accurately. However, there has been considerable work done by such men as Rose, Denny-Brown and Robertson, Simons, and Langworthy, Kolb, and Lewis, by the use of various types of cystometers and other ingenious devices, on the hydrodynamics of the bladder and the relations of the sphincters thereto. Recently there has come to our attention an article published by Sigematu in a Japanese journal in 1940. Sigematu undertook to measure the urinary flow by the use of a "slit-flow-clock apparatus." No charts, illustrations, or numerical data are given. Correlation between volume and time is not made. While this method, as nearly as we can tell from the meager description, should afford a means of measuring the urinary flow, the author did not deem it worth while to report any extended series of clinical cases, and expressed his opinion that the procedure was of little diagnostic value.

The problem appeared to be: 1) To design an apparatus that would measure the minute-volume of urine as expelled per urethram; 2) to establish normal rates; 3) to study the variations from normal in various diseases of the bladder and urethra. This paper is a preliminary report.

An apparatus was required which would enable one to calculate the speed at which the bladder was capable of emptying itself through the urethra in terms of minute-volume. Several types were considered. Apparatus involving a turbine or propeller were abandoned because of the inertia and resistance of the apparatus, and the error resulting from a small stream of high velocity and a large stream of low velocity giving the same reading. This led to the idea of a machine that would measure the increasing weight of urine passed, recorded against a time factor.

The materials used were a toy erector set, and a section of screen door spring, fig. 1, 2*a*. From these was made a balance with the spring attached to one arm

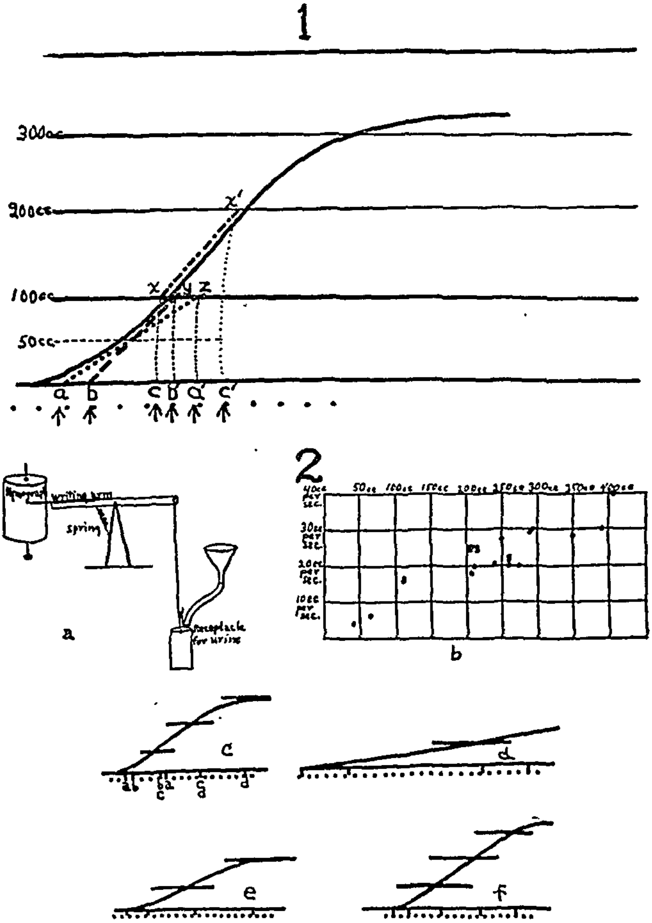

FIG. 1. *1*, Diagram of uroflogram. *See text for explanation*

2, *a*, Diagram of uroflometer (from which time recording device has been omitted). *b*, Chart showing correlation between the volumes and maximum rates attained in 23 voids by one individual. *c*, Normal uroflogram. M.s.v. is 30 cc. *d*, Uroflogram of A.R.H. 2 months after passage of a filiform and 24 F. sound for postoperative stricture. M.s.v. is 7 cc. *e*, Uroflogram of A.R.H. 7 months later after treatment by dilatation, 4 weeks having elapsed since most recent treatment. M.s.v. is 16 cc. *f*, Uroflogram of A.R.H. taken same day as in *e*, but after passage of sounds up to 29 F. M.S.v. is 23 cc.

and a cylindrical metal receptacle of 1000 cc capacity suspended from the other arm. A recording pen was wired to the spring arm. A large funnel and a section of 1 inch rubber tubing was used to conduct the urine to the can. As the can filled that arm was pulled down against the pull of the spring on the opposite side. The apparatus was modified for female use by placing the funnel under a chair fitted with a toilet seat.

A kymograph was placed with a time recording device so that a record of the increasing weight of the urine and the time interval were recorded simultaneously. By calibrating the kymograph paper in 100 cc intervals, drawing a tangent to any part of the curve in which one was interested and projecting to the time line the intersections of this line with the horizontal calibration lines, the number of seconds required for the passage of 100 cc at this rate was obtained. By dividing 100 by the number of seconds in the interval, the rate in terms of cubic centimeters per second was obtained. This was called the second volume. The apparatus was called the uroflometer, and the curves produced designated as uroflograms.

For the sake of convenience the curves have been broken down into segments. The segment representing from 0 to 50 cc is called "a"; the segment representing from 50 to 100 cc, "b"; the segment from 100 to 200 cc, "c"; and each succeeding 100 cc by succeeding letters of the alphabet.

Figure 1, *1* is a diagram of a uroflogram. The method used to compute maximum velocities for the various segments of the curve is as follows: A line a, z, is drawn tangent to the steepest portion of the curve representing the first 50 cc of urine passed intersecting the base line at a and the 100 cc calibration line at z. The point z is projected to the base line at a′. The arrows immediately below these points, i.e. a and a′, represent the projection of these points to the time line. Each dot on the time line represents one second. The number of seconds between these arrows is 5.1. By dividing 100 by 5.1, the maximum second-volume for the first 50 cc is obtained, 19.6. A line b, y, tangent to the steepest portion of the curve representing the second 50 cc of urine passed is drawn intersecting the base line at b, and the 100 cc calibration line at y. The intersection at y is projected to the base line at b′. The arrows immediately below b and b′ represent the projection of these points to the time line. The number of seconds between these points is 4.1. By dividing 100 by 4.1, the maximum second-volume for the second 50 cc of urine passed is obtained, 24.3. Similarly, the line x, x′, is drawn tangent to the steepest portion of the curve representing the second 100 cc of urine passed, and intersecting the 100 cc calibration line at x and the 200 cc calibration line at x′. These points are projected to the base line at c and c′. As before the arrows immediately below these points represent their projection to the time line. The number of seconds between these points is 2.5. By dividing 100 by 2.5 the maximum second-volume for the second 100 cc passed is obtained, 40. In this case this last figure is the maximum second-volume for the entire curve. Henceforth, this maximum second volume will be designated as m.s.v.

The accuracy of the spring was checked repeatedly and new calibrations made with each check. However there has been an accrued change of only about the width of the pen line in 500 cc during 6 months.

Originally graphs of the urination of 155 presumably normal young males were assembled and a study made. Volumes of urine passed ranged from 3 to 560 cc. Fig. 1, *2*, *c* shows a normal curve. It will be noted that there is a slow rise in the curve for the first 50 cc until a maximum rate has been obtained. The maximum rate is normally found in the "b" portion of the curve. There is a slow decline in rate after this until near the end of the void at which time there is a rapid decline to cessation. This is in keeping with the known physiology of the bladder. Denny-Brown and Robertson showed that the pressure in the bladder is rising in the first part of voiding, that it reaches its maximum shortly after voiding commences, and that thereafter it falls gradually until near the end of the void when it falls rapidly.

Maximum velocities calculated ranged from 3 to 50 cc per second. A breakdown of these results dividing them into groups according to the volume passed is shown in table 1. It will be noted that the average rates for volumes under 200 cc are much lower than the average rates for volumes above 200 cc, and that the rates both mean and average for above 200 cc are above 20 cc per second. As a result of this study the figure 20 cc per second was taken tentatively to represent the normal maximum velocity. A more recent compilation with 28 more graphs shows no significant change. This compilation shows that for volumes over 200 cc, 70 per cent or more of the graphs show maximum rates of 20 cc per second or better.

TABLE 1. *A breakdown of maximum rates as found in a study of voiding curves of 155 supposedly normal males*

NUMBER OF CHARTS	VOLUME BETWEEN	HIGH	MEAN	LOW	AVERAGE
		cc./sec	*cc/sec*	*cc/sec*	*cc/sec*
27	00–99	20	9	3	9.1
51	100–199	37	16.6	5	18.7
48	200–299	45	22.2	12.5	24.5
17	300–399	50	23.8	16.0	26.8
11	400–499	38.4	23	16.6	23.8
2	500–599	33.3		16	24.6

A study of 23 charts made by the same individual was made in an effort to study the constancy of rate for a given volume in a given individual and the variation found in different volumes. The maximum rates for the various volumes are shown in figure 1, *2*, *b*. It will be noted that there seem to be quite constant maximum rates for any given volume, and that there seems to be a definite direct relationship between the amount voided and the velocity. It will be noted further however that the maximum volume passed was only 410 cc so that the bladder was never overdistended. That the rate may decline after a certain volume is reached has not been proved but it may be suggested by the fact that the highest maximum rate average was found in the group passing between 300 and 399 cc of urine (see table 1).

Other factors in addition to volume that affect the rate include the state of turgescence of the penis, and psychic factors. A voiding curve made with the penis in a state of partial or complete erection would show a slower than normal rate. The presence of others watching a person void can so inhibit his act as to produce a very low curve. On the other hand, higher than normal rates are obtained if the patient is kept waiting in the presence of running water before being allowed to void.

After the establishment of tentatively normal rates, the rates in persons with definite disease were studied. The curves in patients suffering from stricture were found to be significantly low. These patients were able to produce better curves immediately after dilatation. The improvement would gradually decrease as time passed so that they might have lost all that they had gained by the end of a month. By means of estimating the rate at frequent intervals, one could estimate the effect of treatment. By taking curves before dilatation one could ascertain the amount of gain the patient had made since the last dilatation. Two cases in point are cited.

A. R. H., a 53 year old white male upon whom a perineal prostatectomy was performed October 31, 1945, returned to the outpatient department in February with complaints of diurnal frequency of every 20 minutes to 1 hour, and nocturia every 2 hours. The volume of urine per void never exceeded 3 ounces. A filiform was passed and the urethra dilated to 24 F. By April 4, the patient was again complaining of decrease in the size and force of his stream. A record of his void showed that a volume of 240 cc was passed with a maximum velocity of 7 cc per second (fig. 1, *2*, *d*). Filiforms and sounds to size 26 F. were passed and the patient voided again. This showed a maximum of 14 cc per second for a volume of 240 cc. Further dilatations were performed on May 6, June 6, July 11, August 1, August 22, and September 12, with a gradual increase in the size of the sounds to 30 F. Four weeks later a record showed a maximum rate of 16 cc per second before instrumentation for a void of 200 cc (fig. 1, *2*, *e*). After the passage of sounds up to size 29 F the rate improved to a velocity of 23 cc per second for a void of 330 cc (fig. 1, *2*, *f*).

E. F., a 51 year old male with a history of gonorrhea, came to the outpatient department with the complaint that his stream had become weak over the past year. A record of the patient's urination showed a maximum rate of 7 cc per second for a void of 430 cc (fig. 2, *1*, *c*). After the passage of filiforms and sounds up to size 16 F. the curve showed a maximum rate of 20 cc per second for a void of 210 cc (fig. 2, *1*, *a*). This patient received dilatations at weekly intervals for 2 months, then at monthly intervals for 2 months, and the last dilatation after 6 weeks. A curve produced after 6 weeks without instrumentation showed a maximum rate of 22 cc per second for a void of 215 cc (fig. 2, *1*, *b*).

The curves of patients suffering from benign hypertrophy of the prostate likewise showed striking deviation from the normal. The following cases illustrate the findings before and after operation.

J. P., a 53 year old male, presented himself with complaints of hesitancy, dribbling, and weak stream since 1931. A record of his urination showed a

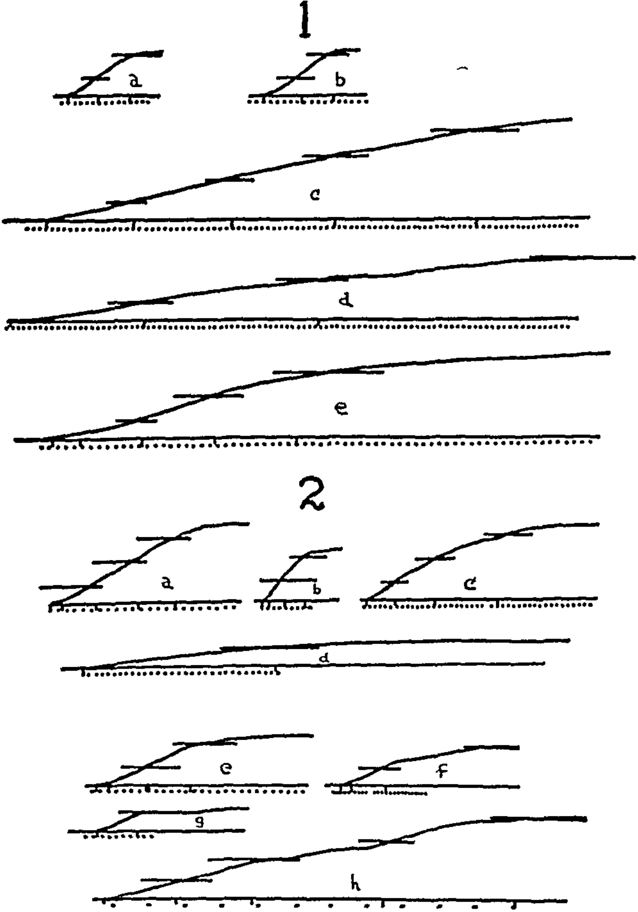

FIG 2 *1*, *a* Uroflogram of E F after passage of filiform and sounds up to 16 F M s v is 20 cc *b*, Uroflogram of E F after 5½ months Patient had received treatment for 4 months but no instrumentation for 6 weeks prior to test M s v is 22 cc *c*, Uroflogram of E F before instrumentation M s v is 7 cc *d*, Uroflogram of J P before transurethral resection M s v is 4 cc *e*, Uroflogram of A G before transurethral resection M s v is 14 cc

2, *a*, Uroflogram of J P 1 week after transurethral resection of prostate M s v. is 30 cc *b*, Uroflogram of A G 5 days after transurethral resection of prostate M s v is 38 cc *c*, Uroflogram of F B 1 week after operation M s v is 18 cc *d*, Uroflogram of F B before transurethral resection M s v is 3 cc *e*, Uroflogram of C L whose large diverticula emptied incompletely after operation M.s v is 21 cc *f*, Uroflogram of A L, a patient suffering from tabes dorsalis and central nervous system lues M.s v. is 9 cc. *g*, Uroflogram of S C, a patient suffering from tumor of bladder M s v is 18 cc *h*, Uroflogram of A H, a patient suffering from tabes dorsalis Time markings on this chart are in 5 second intervals M.s v is 9 cc.

void of 290 cc with a maximum rate of 4 cc per second (fig. 2, *1*, *d*). Rectal examination revealed a bilateral enlargement of the prostate. Cystoscopy showed a large median bar and moderate intrusion of the lateral lobes. Transurethral resection was performed. A record made 1 week postoperatively showed a void of 350 cc with a maximum velocity of 30 cc per second (fig. 2, *2*, *a*).

F. B., a 68 year old male, was seen in a physician's office with complaints of nocturia 4 to 5 times, hesistancy, interruption in voiding, and decrease in the size and force of his stream. The prostate gland was 1½ times normal size by rectal examination. Transurethral resection was performed. A record of his voiding before operation showed a maximum flow of 3 cc per second for a volume of 130 cc (fig. 2, *2*, *d*). The bladder contained 300 cc residuum at this time. One week after operation the patient was able to void at a maximum rate of 18 cc per second for a volume of 330 cc (fig. 2, *2*, *c*).

A. G., a 51 year old male with complaints characteristic of benign hypertrophy of the prostate, preoperatively was able to void 380 cc at a maximum rate of 14 cc per second (fig. 2, *1*, *c*). Five days after transurethral resection, the record showed a void of 230 cc with a maximum velocity of 38 cc per second (fig. 2, *2*, *b*).

Under the heading of "neurogenic" bladder the only group that lends itself to study are of the atonic paralytic type. In the hypertonic type the patient usually cannot pass enough urine to produce a readable curve. The following cases illustrate our findings to date.

A. H., a 60 year old female, was admitted with a complaint of epigastric pain, burning, and discomfort since 6 p.m. the night previously. For the past 15 years she had had burning or cutting pain of a shooting nature that began at the toes, settled in the epigastrium, and produced vomiting. These episodes occurred every 4 months and lasted 2 to 3 days. The patient had nocturia 1 to 2 times and no urethral burning. The cystometric reading was low, showing a rise to only 6 mm mercury after the instillation of 800 cc. There was no increase upon attempting to void without straining, but the pressure rose to 62 mm. mercury upon attempting to void with straining. Slow distension to 900 cc produced no pain. The diagnosis was tabes dorsalis. A curve of the void showed a maximum velocity of 10 cc per second for a volume of 420 cc. The maximum rate for the last 220 cc was 5.2 cc per second (fig. 2, *2*, *h*).

A. L., a 45 year old male, was admitted with the complaint of being unable to walk without the aid of crutches. He had no nocturia, and only occasional burning. He experienced some desire to void before a bowel movement, but this disappeared after the movement without the patient's having voided. A record of urination showed a maximum velocity of 9 cc per second for a void of 210 cc (fig. 2, *2*, *f*). A residuum of 60 cc was present after this void. Cystometric test showed a large atonic bladder with a capacity of 1150 cc. No discomfort was experienced until 1000 cc had been instilled and the pressure had risen to 21 mm. mercury. Final diagnosis was central nervous system syphilis and tabes.

Two other patients with degenerative lesions of the cord produced curves showing rates of 11 and 12 cc per second for volumes of 330 and 420 cc, respectively.

K. S., a male aged 59, had urinary retention after an abdomino-perineal resection for carcinoma of the rectum. The curve of his void showed a rate of 5.5 cc per second maximum for a void of 160 cc. Following transurethral resection of the bladder neck, this patient voided 150 cc at a maximum rate of 10 cc per second.

Two cases are presented in which the maximum rates are not significantly low but in which other abnormality is present.

C. L., a male aged 76 years, was subjected to transurethral resection for enlargement of the prostate. After operation the patient still carried a residual urine of 300 cc. He was known to have large diverticula. The curve produced by this patient's urination showed a maximum rate of 21 cc per second for a void of 230 cc. The remarkable finding was a sudden slowing of the rate after the passage of 190 cc, and the slow passage of the next 40 cc (fig. 2, *2*, *e*). Roentgenograms taken at the moment of slowing and post-evacuation show that this slow rate is due to partial emptying of the diverticula.

S. C., a male aged 31, presented himself with the complaint of hematuria of 10 years' duration, occurring at 6 month intervals and lasting 24 hours. Rectal examination revealed a prostate of normal size and consistence. Cystoscopic examination showed a relatively large pedunculated bladder tumor. The curve of urination showed a void of 115 cc with a maximum velocity of 18 cc per second. The rate of passage of the last 15 cc was exceedingly slow, about 1 cc per second (fig. 2, *2*, *g*). It is possible that the presence of the tumor mass interfered in some way with the action of the detrusor muscle. It is also possible, though not proved, that the tumor mass fell over the vesical orifice during the late stage of the void.

In making this preliminary report it is realized that the subject has not as yet been fully studied. However it is believed that this report may give some indication of what the final result of the investigation will be. The study has been confined largely to males because of difficulty in obtaining women subjects for normals. Only maximum rates and curves showing fairly normal distribution of velocities have been used in this study, although much information may be obtained from the study of the average rates or a correlation of the voiding time and the amount of urine passed. Curves showing as many as 5 increases and slowings in rate have been produced. Some show maximum rates toward the end of the curve. As these have not been numerous, and their significance is not yet clear, a discussion of them has been deferred. The choice was made because it seemed desirable to work with the maximum capacity of the bladder and urethra.

The apparatus used is crude and simple in design, but at the same time quite accurate.

The number of subjects used for the establishment of normal rates is admittedly low. However a figure well below average for the group has been chosen as low normal. In spite of this fact the deviations in maximum rates in patients suffering from diseases of the bladder and urethra are sufficiently great that there is little chance that they may be confused with the normal. Low curves of this type have been found in patients having stricture, contracture of the vesical orifice, enlargement of the prostate, and neurogenic bladder. Curves showing abnormal distribution of velocities have been found in conditions causing interference with normal emptying of the bladder, such as tumor or diverticula.

It is believed that this method of investigation may be useful in making diagnoses of stricture, benign hypertrophy of the prostate, neurogenic bladder, and other diseases of the bladder and urethra, and particularly in making early diagnoses in doubtful cases. It may serve to detect cases of congenital contracture of the vesical orifice in which the weak stream, having always been present, is regarded by the patient as normal. It may find its greatest usefulness in the sorting out of patients with disease of the bladder and urethra in the routine examination of large numbers of subjects such as was carried out in Army induction centers. It is also an excellent method by which to evaluate the results of treatment. If for example a maximum rate of 18 cc per second is observed after a transurethral resection, the result is definitely unsatisfactory even if the patient at the moment has no complaints. Its chief feature in the field of urologic diagnosis is the objectiveness of the test and the fact that it involves the passage of no instruments with the dangers inherent in such passage.

SUMMARY

An apparatus has been described that will enable one to compute the volume-time relationship in the flow of urine through the urethra. It is called the uroflometer.

A study of 155 normal males is described and a limit selected to be considered the dividing line between normal and lower than normal rates.

Case reports illustrating the usual findings in patients suffering from stricture of the urethra, benign hypertrophy of the prostate, neurogenic bladder, diverticula of the bladder and bladder tumor are presented.

It is uggested that the uroflometer may prove valuable as a diagnostic aid and as a means of evaluation of the results of treatment without resorting to instrumentation.

I wish to express my thanks to Dr. D. M. Davis for his inspiration and encouragement in this research.

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A CLINICAL EVALUATION OF A RECENT SULFONAMIDE: Nu-445

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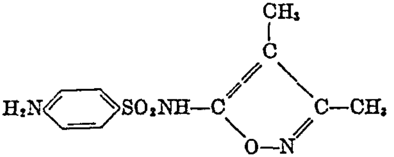
Nu-445 is a recent drug of the sulfonamide group having this chemical formula—



3,4-dimethyl-5-sulfanilamido-isoxazole

The drug has been recommended as an effective agent against gram negative infections of the urinary tract. This study was undertaken to evaluate the efficiency of this preparation against such organisms.

Our interest in this new drug[1] developed following a publication by R. J. Schnitzer et al. of their observations following its use in animals. They gave rabbits 0.794 gm. per kilo of Nu-445 daily and found blood sulfonamide levels of from 10 mg. per cent to 20 mg. per cent. They also found that 43 to 61 per cent of the drug given orally was eliminated through the kidneys and 68 per cent in the unacetylated form. Impressed by the marked solubility of the drug and by the total absence of renal irritation this group then studied the effect of the preparation on gram negative organisms. The results suggested that the drug might be of value in the treatment of infections caused by such organisms.

Recently Sarnoff and others published the results of a clinical trial of Nu-445. They were interested only in the effect of the drug on the B. proteus which was present in every case with a variety of other organisms. The dosage varied from 50–112 gm. in most instances given over a period of 10 days. In their series of 14 cases they were encouraged by the fact that 11 were favorably influenced and in 9 the B. proteus disappeared from the cultures.

Our studies cover a group of 20 patients with urinary infections due to various gram negative organisms, chiefly E. coli, B. proteus, and B. pyocyaneus. Before starting treatment cultures from the urine or wound were planted on blood agar and endo agar. The usual check was made of the urinary sediment, the hemoglobin, and the blood count. In addition, the infecting organisms from many of the patients were tested for their sensitivity to Nu-445 in vitro. Here it was found that the effectiveness of the drug was enhanced when the pH of the media was between 7 and 8. At this level growth of B. pyocyaneus ceased at a concentration of 3.1 mg. per cent of Nu-445 while at a pH of 5 a level of 6.2 mg. per cent was necessary for bacteriostasis. For this reason the urines of all the patients receiving the treatment were made alkaline by sodium citrate. With above figures in mind, however, it was apparent that a therapeutic urinary drug concentration could be maintained only by administering rather large doses of the preparation since approximately 50 per cent was excreted through kidneys.

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[1] Nu-445 was supplied by the Hoffman-La Roche Laboratories.

Initially the patients were given the recommended dose of 4 gm. daily but when the blood sulfanilamide level rose to only 3.7 mg. per cent and it was apparent that severe toxic reactions were not appearing the dose was increased to 8 gm. This was not accompanied by a corresponding rise in the blood level. The highest concentration that appeared in the urine was 35 mg. per cent. Later a group of 5 patients were given daily doses of 12 gm. All of these individuals developed satisfactory urine drug levels comparable to those observed by Schnitzer and his group.

CASE REPORTS

To illustrate some of the problems and the results obtained when doses up to 8 gm. daily were given a few of the histories are recorded.

Case 1. A 38 year old white woman was transferred to the urological service from the surgical service after recovery from an operation for chorionepithelioma. During the operation an enlarged right kidney was palpated and subsequently found to be hydronephrotic due to an obstruction at the ureteropelvic junction. The initial urine culture grew moderate E. coli and abundant non-hemolytic streptococci. Urine obtained at cystoscopy on November 6, 1946 was sterile. On November 13 the kidney was explored and a Foley type pyeloplasty performed. A nephrostomy tube and splinting catheter were inserted, the latter being removed on the fifth postoperative day and the former on the eleventh day. Urine cultures with the tubes present grew abundant E. coli and a few colonies of B. proteus. At the time the last tube was removed she was started on 8 gm. of Nu-445 and 4 gm. of sodium citrate daily. These were continued over a period of 10 days. The B. proteus was eliminated after the first day of therapy. The colonies of E. coli were present in diminishing numbers until the ninth day when the urine became sterile. The most recent urine culture on December 19 showed a few colonies of E. coli. The patient had no toxic symptoms.

Case 2. A 23 year old white male was admitted to the urological service with recurring fever and chills and pain in the left flank due to pyonephrosis of several years duration. Cultures of the urine from the bladder and left kidney grew abundant B. pyocaneus. The infected kidney was removed on December 30, 1946 and because of the continued presence of abundant growth of B. pyocyaneus in the urine, Nu-445 in a dose of 8 gm. with sodium citrate was begun. On the fourth day of treatment the urine cultures became sterile and remained so.

Case 3. A 63 year old white male was admitted to the urological service on July 21, 1946. He had been bothered with severe burning and frequency of urination for several months. Detailed study failed to demonstrate a reason for the cystitis. There was no bladder neck obstruction. He was treated with Nu-445 over a period of 10 days and received a total of 60 gm. On the ninth day the B. proteus disappeared but E. coli continued to be present in abundance. Toxic symptoms manifested by temperature elevation to 101° appeared on the ninth day of treatment and subsided when the medication was discontinued. The E. coli infection persisted but disappeared after 2 days of treatment with streptomycin.

Case 4. A 75 year old white male was admitted to the urological service on September 30, 1946 in acute urinary retention due to benign prostatic hyperplasia. On October 5 a perineal prostatectomy was done. During the procedure the rectum was accidentally torn. The laceration was closed satisfactorily but not without contamination of the field. The patient did well postoperatively and although the rectum and urethra healed cleanly the urine was grossly infected with E. coli. He was treated with Nu-445 over a period of 28 days during which time he received a total of 168 gm. The urine at the end of this time contained only a few pus cells while a rare colony of E. coli grew in the cultures.

TABLE 1

CASE	Nu 445	BLOOD LEVEL		URINE LEVEL		24 HOUR URINE VOL.	INITIAL CULTURE	FINAL CULTURE
		Free	Total	Free	Total			
	grams	*mgms %*	*mgms %*	*mgms %*	*mgms %*	*cc*		
#16	168	3.7 5.0	5.6 6.5	448	480	3250	E. coli ++++	E. coli ++++
#17	96	3.5 5.6	6.5 6.9	656	776	1980	E. coli ++++ N. H. Strept +	E. coli ++++ B. pyocyaneus ++++
#18	84	4.1	5.8	568	869	1650	E. coli ++++	E. coli + Staph. alb. +
#19	96	3.6 6.0	7.2 7.4	622	1052	1150	E. coli ++++ B. pyocyaneus +	E. coli ++++
#20	108	2.0 1.7	3.2 3.1	85	103	4330	E. coli + Staph. alb. +	N. H. Strep. ++++ B. pyocyaneus +

The remainder of this group which received the drug in amounts varying from 40 to 80 gm. showed no improvement. Four had pure cultures of E. coli and one of B. pyocyaneus, while the other 3 had mixed infections of these organisms in combination with B. proteus. Previously all of these individuals had been treated with adequate doses of other sulfonamides without benefit.

Complicating factors occurred in 5 patients but only 3 were unable to continue with the medication because of toxic symptoms. The elevation of temperature in case 3 forced the withdrawal of the drug while in another patient erythema developed. One patient could not continue with the drug because of nausea. Of the patients whose symptoms were not ascribed to the medication,

RENAL COMPLICATIONS OF HYPERPARATHYROIDISM[1]

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Considerable information regarding the activity of parathyroid adenomas has been made available from the more than 300 recorded cases[2]. The parathyroid tumor is a benign lesion. From the standpoint of endocrinology it is an active tumor and disturbs the body economy by producing an excess amount of parathyroid hormone leading to a disease presently recognized as primary hyperparathyroidism. The metabolic abnormalities concern chiefly calcium and phosphorus concentrations. The serum calcium is increased whereas the serum phosphorus is decreased and both calcium and phosphorus are eliminated in abnormally large amounts in the urine.

The clinical importance of these metabolic disturbances centers chiefly around symptoms arising from alterations in the skeletal system and renal complications resulting from calcium deposits in the urinary tract. The skeletal changes lead to a group of special symptoms based upon decalcification of bone. The nature of these is often disabling but does not necessarily endanger life. The symptoms which arise from the urinary tract vary somewhat according to the type of renal involvement and the degree of impaired renal function. Albright and his associates[3] have described three ways in which the kidneys may be involved in hyperparathyroidism and they refer to these as types I, II and III. They describe types I and III first. Type I is described as "pyelonephritis secondary to formation of calcium phosphate stones in the renal pelvis." Type III is defined as "acute parathyroid poisoning with anuria and death from undetermined cause in a few days, with calcium deposits in kidney parenchyma as well as in other organs, but with no chronic renal changes." Type II is "a condition midway between these two which simulates both chronic glomerular and vascular nephritis. It differs from type I in that the deposits are in the kidney parenchyma rather than in the kidney pelves and from type III in that the kidneys show longstanding changes and may be the only organs involved in the calcium deposits."

Hyperparathyroidism is not a common disease. Chute[4], who reviewed the records at the Massachusetts General Hospital over a 10 year period from 1930 to 1939 inclusive, found a total of 36 cases in more than 62,000 hospital admissions, so that the incidence for that institution was slightly less than 1 case for each 1500 admissions. Thirty or 83 per cent of these patients had renal calculi. During a 5 year period from 1942 to 1946 inclusive, in slightly more than 57,000 admissions to the Ochsner Clinic, we recognized 4 cases of hyperparathyroidism, all with renal complications. It seems likely, if the incidence is the same in different localities, that a number of cases have passed through our hands unrecognized. These 4 cases are reported first, to add them to the growing list of recorded cases and second, to emphasize some of the problems encountered in treatment.

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[1] Read at annual meeting, Southeastern Section, American Urological Association, Palm Beach, Fla., March 26–28, 1947.

[2] Norris, E. H.: The parathyroid adenoma. A study of 322 cases. Internat. Abstr. Surg. 84: 1–41, 1947 in Surg., Gynec. & Obst. 1947.

[3] Albright, F., Baird, P. C. and Bloomberg, E.: Studies on the physiology of the parathyroid glands. IV. Renal complications of hyperparathyroidism. Am. J. M. Sc. 187: 49–65, 1934.

[4] Chute, R.: Clinical aspects of hyperparathyroidism with special reference to urology. J. Urol. 41: 762–772, 1939.

CASE REPORTS

Case 1. F. T., a 57 year old white man, was admitted on March 3, 1942, complaining of symptoms referable primarily to the urinary tract, polyuria and pain in the region of both kidneys. Other symptoms were polydipsia, weakness, easy fatigability, nervousness and constipation. He had never passed a stone.

Urinalysis showed albumin, hyaline casts, amorphous sediment and red blood cells but no infection. The result of the phenolsulphonphthalein test was 40 per cent for 1 hour and 10 minutes. Roentgenograms of the urinary tract (fig. 1, *A*) showed calcium deposits in the collecting tubules throughout the cortex of both kidneys. Since the distribution of calcium in the kidneys suggested hyperparathyroidism, other appropriate studies were carried out. Serum calcium was reported as 16 mg., 16 mg. and 15 mg. per 100 cc. of blood in three separate determinations. The serum phosphorus determinations done at the same time were reported as 3.1 mg., 2.6 mg. and 2.6 mg. per 100 cc. of blood. Roentgenograms of the skeletal system showed no evidence of decalcification.

The neck was explored and a parathyroid adenoma was removed from the region of the left inferior parathyroid gland. The serum calcium 2 days following operation was reported as 11.2 mg. per 100 cc. of blood and on the eleventh postoperative day it was 7 mg. per 100 cc. of blood.

In this type of renal involvement it is hoped that removal of the parathyroid adenoma will arrest the progressive damage to renal function. Disappearance of the calcium deposits from the renal cortex and improvement in renal function will not likely occur.

This patient has been followed over a period of almost 5 years and his kidneys have apparently suffered no further damage. Roentgenograms of the urinary tract on September 18, 1946, showed no change in the calcium deposits in the kidneys (fig. 1, *B*). The result of the phenolsulphonphthalein test was 40 per cent and the serum calcium determination was 10.2 mg. per 100 cc. of blood. The patient was asymptomatic and appeared well.

Case 2. Mrs. R. S., a 70 year old white woman, consulted us on September 27, 1946, because of symptoms referable to the skeletal system. Her chief complaint was pain in the right side and hip. She had noticed an increased bowing of her legs with consequent decrease in height over a period of 15 years.

Both wrists were fractured in a fall 7 years before but the trauma was apparently sufficient to break normal bones.

The patient had a palpable, smooth, freely movable tumor in the right side of the neck, fine calcium deposits in both kidneys, bowing of the femur (fig. 2, *A*) and patchy decalcification of the skeletal system. There was a large area of decalcification in the right ilium. The skull showed moderate osteoporosis with several small cystic changes especially at the vertex and right frontal bone (fig. 2, *B*). From a roentgenographic standpoint the findings were consistent with those of long standing hyperparathyroidism.

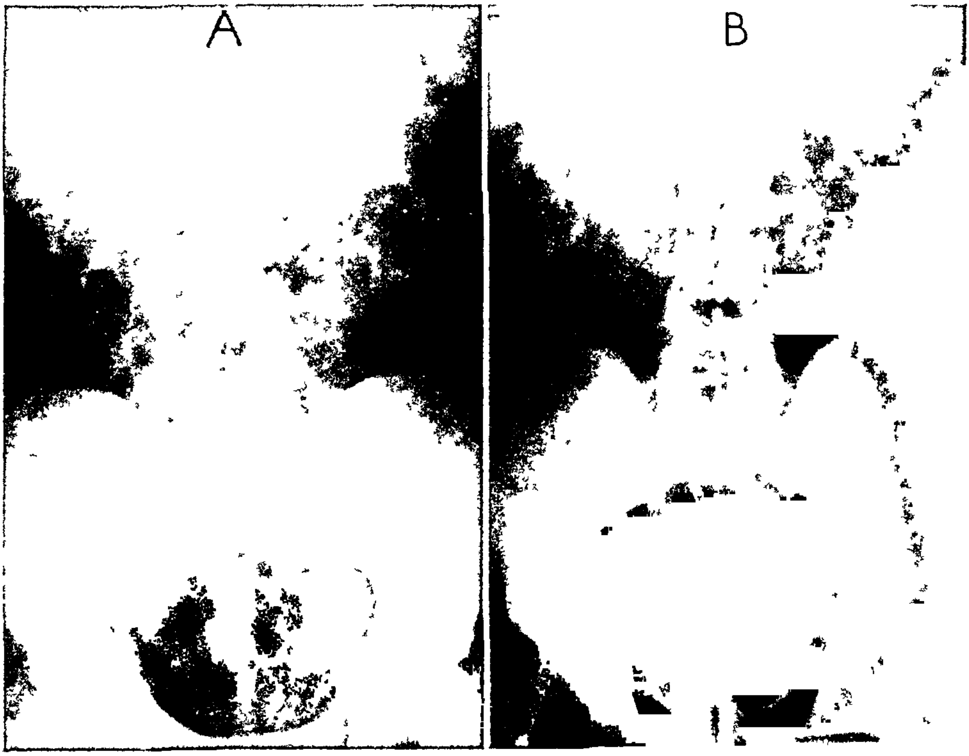

FIG. 1. Case 1. *A*, Roentgenogram of kidney, ureter and bladder, showing calcium deposits in collecting tubules throughout cortex of both kidneys. *B*, Roentgenogram of kidney, ureter and bladder showing fine calcium deposits in cortex of both kidneys

Blood studies showed a serum calcium level of 12.8 mg. and serum phosphorus 1.1 mg. per 100 cc of blood and, when repeated, serum calcium 13 mg. and serum phosphorus 1.4 mg. per 100 cc. Blood urea nitrogen was 24 mg. per 100 cc. The urine was infected and showed albumin and casts.

Exploration of the neck was advised but operation was refused by the patient and her family. In view of the skeletal changes and calcium deposits in the kidneys together with increased serum calcium and decreased serum phosphorus and a palpable mass, in the neck we feel justified in reporting this case as one of hyperparathyroidism even though the diagnosis was not confirmed by removal of a parathyroid tumor.

Case 3. Mrs. A. H., a white woman aged 42, was admitted May 14, 1946, because of symptoms referable to the urinary tract. There had been repeated attacks of bilateral renal colic over a period of 4 years and many stones had been passed. Some of the recent attacks had been accompanied by chills and fever. The patient had noticed abdominal discomfort and nausea after exercise for 20 years.

Significant findings were colon bacillus infection of the urinary tract, a slightly enlarged and tender left kidney, multiple stones in the left lower ureter and 3 stones in the right kidney (fig. 3). There was moderate impairment of renal function.

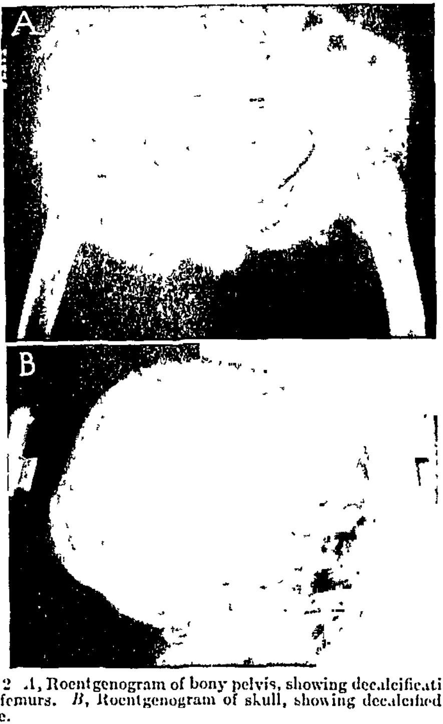

Fig. 2. Case 2 *A*, Roentgenogram of bony pelvis, showing decalcification in right ilium and bowing of femurs. *B*, Roentgenogram of skull, showing decalcified areas in vertex and frontal bone.

The serum calcium determination was 13.1 mg. and serum phosphorus 2.6 mg. per 100 cc of blood. These studies were repeated with reports of serum calcium 13 mg. and serum phosphorus 1.6 mg. per 100 cc of blood. There were no skeletal changes. A clinical diagnosis of primary hyperparathyroidism with secondary renal and ureteral calculi was made.

Because of the recent attacks of pain in the left side with chills and fever, removal of the calculi in the left lower ureter appeared first in order of indications for treatment. The stones in the ureter were removed by cystoscopic manipulation, multiple catheters being used. On June 13, 1946 the neck was explored and a parathyroid adenoma was removed from the region of the right inferior parathyroid gland (fig. 4). Blood studies in the immediate postoperative period showed serum calcium 9.8 mg. and serum phosphorus 1.8 mg. per 100 cc of blood. Stones were removed from the right kidney on November 7, 1946. Recovery from each operative procedure was without complication.

The patient reported for check-up examination on February 25, 1947. The serum calcium was 10 mg. and the serum phosphorus 1.8 mg. per 100 cc of blood. The renal function showed improvement after removal of the stones but the urine remained infected.

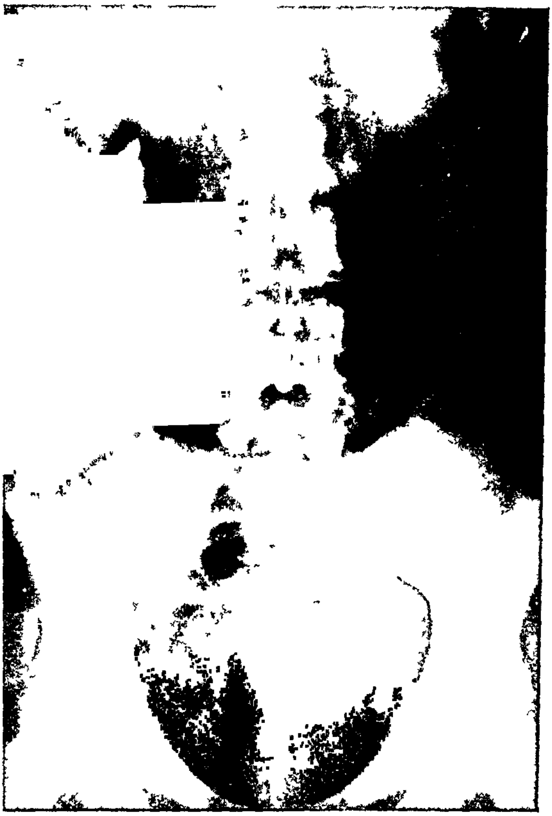

FIG. 3. Case 3. Roentgenogram of kidney, ureter and bladder showing multiple stone in left lower ureter and 3 stones in right kidney. There were no skeletal changes.

Case 4. S. J. T., a 42 year old white man, was admitted on July 26, 1944, because of symptoms radiating from the urinary tract. He had the first attack of renal colic in 1926. During the next 15 years he had repeated attacks on both sides and passed many small stones. He had severe pain in the right side in 1941 when roentgenograms, made for the first time, showed a large stone in the right kidney and small shadows in the region of the prostate. The left kidney was said to be normal. From 1941 until we saw him in 1944 he had repeated attacks of pain in the right renal area associated with chills and fever. There was no history of fracture or long periods of immobilization. The patient did not drink milk and gave no history of excessive ingestion of alkalis except for a period in 1941 when he took vitamin D concentrate and large glasses of orange juice daily for a period of several months. His mother had a bladder stone but otherwise there was no history of stones in his family.

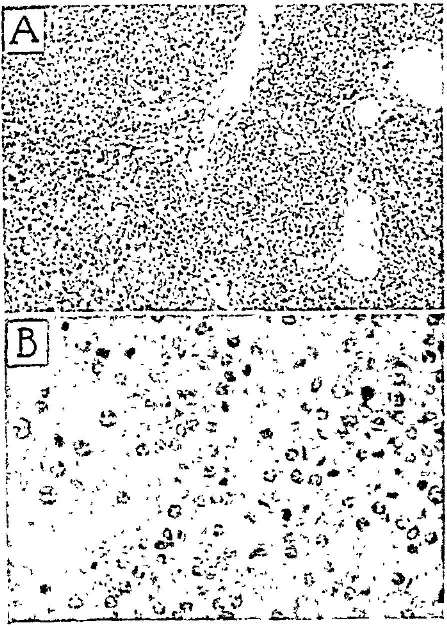

FIG. 4. Case 3. *A*, Parathyroid adenoma removed at operation (× 80). Typical area in adenoma, showing *diffused hyperplasia of chief cells. In some areas* cells are arranged in patterns simulating alveoli. Generally they are found in compact cords with pale cytoplasm " Parathyroid adenoma removed at operation (× 40 of chief cells with deeply staining nuclei and pale, .

The urine was cloudy, pH 6.5, specific gravity 1.010 and the stained slide showed pus and gram-negative bacilli. On culture staphylococci and colon bacilli were reported. These organisms did not split urea. The right kidney was large and tender. Roentgenograms of the genito-urinary tract showed a shadow 1.7 by 3 cm. in the region of the right kidney and multiple small shadows in the prostatic area (fig. 5, *A*). There were no shadows in the left renal area or along the course of the left ureter. Intravenous urograms showed a normally functioning left kidney but there was no apparent concentration of the dye on the right side (fig. 5, *B*). No changes in the skeletal system were noted. We did not at this time suspect hyperparathyroidism. It was assumed that the patient had a large pyonephrotic right kidney and he was advised to enter the hospital for further study and possible nephrectomy. For business reasons this had to be postponed.

Following another attack of pain on the right side with chills and fever the patient entered the hospital on September 19, 1944. Ten ounces of hazy urine was aspirated from the right renal pelvis when the right ureter was catheterized. The catheter was left indwelling for relief of renal block. The left ureter was purposely not catheterized for fear of infecting the left kidney which it was hoped had not become infected. Cultures from the right kidney showed the same organisms as those previously cultured from the bladder urine. Thirty minutes after the intravenous injection of 10 cc of indigo carmine, only a trace of the dye appeared from the right kidney. Roentgenograms at this time showed the same findings as those previously noted.

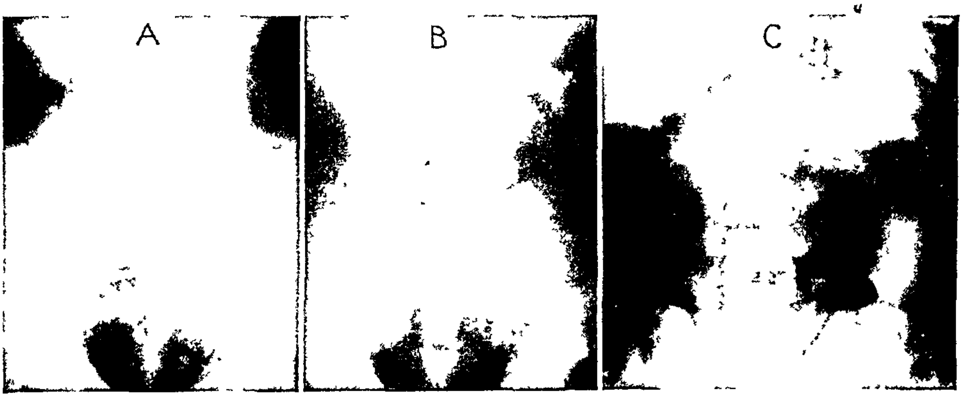

FIG. 5. Case 4. *A*, Roentgenogram of kidney, ureter and bladder, showing stone 1.7 by 3 cm. in right kidney. *B*, Intravenous urogram, showing normal function of left kidney and nonfunction of right kidney. *C*, Roentgenogram of kidney, ureter and bladder, showing multiple stones in left kidney 6 weeks after operation.

Two days later subcapsular removal of a large pyonephrotic kidney together with the stone was done with comparative ease. The postoperative course was complicated on the tenth day by a chill and rise in temperature up to 103 F. There was no pain. The temperature returned to normal 4 days later and the patient was discharged in good condition on the twentieth postoperative day. Analysis of the stone showed calcium phosphate. During the postoperative period he was given mandelic acid, sulfa drugs and penicillin but the urinary infection showed no improvement.

Six weeks after nephrectomy the patient had slight discomfort in the left side and passed 3 small stones. Roentgenograms at this time showed several stones in the left kidney (fig. 5, *C*). In view of negative findings on urea cultures and the rapid formation of stones a metabolic disturbance was considered for the first time. Four serum calcium determinations were done during the next 10 days. The reports were 14.9 mg., 15.8 mg., 13.2 mg. and 13.3 mg. per 100 cc of blood. The serum phosphorus was 2 mg., 2.5 mg., 2.1 mg. and 2.6 mg. per

100 cc of blood during the same period. The patient was put on Albright's neutral low calcium diet for 6 days. The urinary calcium excretion showed 414 mg. and 404 mg. for each of two 24 hour periods. Normal urinary calcium excretion on this diet is between 100 and 200 mg. in 24 hours.

It was apparent from these studies that this was a case of hyperparathyroidism and the patient was referred to the surgical service for exploration of the neck. This was done on December 21, 1944 and a small tumor was removed from the region of the right superior parathyroid gland. A careful search of the thyroid and other parathyroid areas revealed no other evidence of parathyroid adenoma. Frozen section of the small tumor was reported to show parathyroid tissue.

TABLE I. *Schedule of roentgen therapy in case 4*

DATE	Ma	KV	STD	FILTER	TIME	r	FIELD
4-2-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
4-3-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
4-4-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
4-5-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
4-6-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
4-7-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
5-21-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
5-22-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
5-23-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
5-24-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
5-25-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.
5-26-45	20	215	50	1 cu & 1 al	8	224	Ant. cerv. & medstnl.*
7-8-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-9-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-10-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-11-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-12-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-15-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-16-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.
7-17-46	20	215	50	1 cu & 1 al	8	226	Ant. cerv. & medstnl.†

* Much improved, no new calculi.

† No more stones.

Serum calcium studies in the postoperative period were disappointing. The reports ranged from 13 mg. to 15 mg. per 100 cc of blood.

Since further search for a parathyroid tumor was considered essential, on February 24, 1945, the mediastinum was explored transternally. A fatty growth was removed from the anterior mediastinum but no other evidence of tumor was found during a careful search of the mediastinal space. Pathologic sections of the fatty tumor showed no evidence of parathyroid tissue. The patient continued to form stones with remarkable rapidity. Most of these passed into the ureter and were removed by cystoscopic manipulation, multiple catheters being used. One stone, which was too large to pass, remained in the lower calyx. At this point the use of deep roentgen-ray therapy was considered although without any great enthusiasm for the results which might be obtained. Irradiation to the anterior cervical and mediastinal areas was started on April 2, 1945. Table I shows the amount of treatment given. Twelve days later the serum calcium was 12 mg. and the serum phosphorus 2.1 mg. per 100 cc of blood. The second series of treatment was finished on May 26, 1945 and in the meantime no new calculi had formed.

On August 17, 1945 the stone was removed from the left kidney and a nephrostomy tube inserted. It was felt that by leaving a nephrostomy tube in place, calcium deposits could be washed out or in case stones formed they could be removed with a Randall type of stone forceps through the nephrostomy opening. The nephrostomy tube was left in place for a year. During this period the kidney was irrigated with mild antiseptic solutions chiefly for the purpose of mechanical cleansing and the tube was changed at intervals. Roentgenograms showed no recurrence of stones and the serum calcium became stabilized at the upper limits of normal. Another series of roentgen-ray treatments was given during July 1946 (table I). The last serum calcium determination on February 15, 1947 was reported as 11.8 mg. per 100 cc of blood. The urine is acid and sterile.

Whether this patient's parathyroid activity has been influenced by irradiation or is in a period of remission will have to be determined by future observations.

DISCUSSION

Primary hyperparathyroidism produces no specific symptoms and the majority of cases are unrecognized until complications of clinical importance have developed. It should be considered a possibility in every case with renal calculi. Hypercalcemia (11 mg. or above) and hypophosphatemia (3 mg. or below) are the two most important laboratory findings. All determinations should be rechecked to avoid error.

Most of the problems involved in the management of patients with renal lesions secondary to hyperparathyroidism have been discussed in the case reports. Surgical removal of the parathyroid adenoma is the only effective treatment. Results from roentgen therapy have as a whole been unsatisfactory. We used it in one of these cases only after surgical exploration of both the neck and mediastinum had failed to remove enough parathyroid tissue to stabilize calcium metabolism. Medical treatment has likewise been unsatisfactory. Except in acute conditions of the urinary tract such as ureteral block the parathyroid tumor should be removed first. The results in the majority of cases are highly satisfactory. The serum calcium level usually drops to normal within 48 hours. The urinary tract complications are dealt with according to present standard urologic procedures. In the case of calcium deposits in the collecting tubules (Albright's type II lesion), it would be interesting to know how many of these patients suffer further renal damage from calcium deposits alone after the parathyroid tumor has been removed. The one case of this type that we have followed for more than 5 years has showed no further renal damage.

SUMMARY

The parathyroid tumor, a benign lesion, disturbs the body economy by producing an excessive amount of parathyroid hormone leading to a pathologic process called primary hyperparathyroidism. The disease produces no specific symptoms and the majority are unrecognized until complications, of which the most significant are skeletal changes and renal involvement, have developed. Hypercalcemia and hypophosphatemia are the most important laboratory findings. The only effective treatment is surgical removal of the parathyroid adenoma. The complications referable to the urinary tract are treated according to present standard urologic procedures. Four cases are described to illustrate the various problems encountered in treatment.

RENAL TUBERCULOSIS WITH SPECIAL REFERENCE TO CASES OF LONG STANDING AND THOSE TREATED WITH STREPTOMYCIN[1]

NELSE F. OCKERBLAD AND ROGER P. WELTMER

"Captain of the men of death" is the descriptive term Sir William Osler borrowed from John Bunyan to characterize pulmonary tuberculosis. Renal tuberculosis is second in frequency to pulmonary tuberculosis. It is no longer "Captain of the men of death" but is is too prevalent to be regarded lightly.

The period of duration elapsed from the time the first patient in this series was first seen until the present moment is 26 years. This is none too long a period in which to evaluate properly and personally study the finding and course of the disease in the patients seen during this quarter of a century.

This study is in reality a kind of Gallup poll taken out of a larger series of renal tuberculosis cases. All of the cases studied cannot be described in individual detail, case by case. Later in this paper the details of four of the most interesting cases will be cited. Thirty cases have been selected more or less at random but having in mind the cases which we have followed for a long period.

In the grouping by sex, there are 20 females and 10 males. This ratio of 2 females to 1 male is not the usual one, for Emmett and Kibler reverse this and find 2 males to 1 female, while Henline reports a 1 to 1 ratio. Perhaps a larger series would change it but the figures in the remainder of this study fall into line so that for our cases, at least, this is true. However, I am inclined to believe that they are correct who say that the disease is evenly divided between the sexes.

Age group

Years	*Number*	*Per cent*
1–9	0	0.0
10–19	4	13.3
20–29	5	16.6
30–39	9	30.0
40–49	7	23.3
50–59	3	10.0
60–69	2	6.0

The age groups are of considerable interest since they follow a pattern that is well known. In fact, here we may compress 69.9 per cent of the cases into an age group 25 to 45 years. There is found a considerable percentage of cases in the second decade. The juvenile cases are of much interest and really deserve special study. That renal tuberculosis occurs in the sixth and seventh decades is well known among urologists, but it is not so generally recognized among other members of the profession. These older individuals are very apt to have low grade chronic infection which they have had for a long time. They generally display considerable immunity to their infection and when sizable masses of tuberculous pathology are amputated, they show remarkable recuperative powers.

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[1] Read at annual meeting, Southeastern Section, American Urological Association, March 26–29, 1947.

The duration of the disease before the patient consulted a urologist for relief is interesting. The longest period was 60 months, or 5 years, and the shortest, 3 months, an average duration of 25.6 months. It is quite common for the patient to have had considerable desultory and misdirected treatment during this interval. Many times the true cause of the patient's symptoms is not even suspected.

Associated disease

	Number	*Per cent*
Epididymitis	4	13.3
Prostatic tuberculosis	2	6.1
Calcified lymph nodes	2	6.1
Hunner's ulcer	3	10.0
Stones	3	10.0
Sinuses	5	16.6
Pulmonary involvement of various degrees	9	30.0
Histoplasmosis	1	3.0
Periureteral abscess	1	3.0
Tuberculosis of spine	1	3.0
Bone tuberculosis	1	3.0
Carcinoma of cervix	1	3.0

All the cases in this group showed some associated disease. Many of the individuals had more than one type of extrarenal involvement.

Epididymitis occurred in 4 cases, 13.3 per cent, and was dealt with by epididymectomy in 3 cases and in the fourth by orchidectomy. Cristol and Greene state that 42 per cent of their series had epididymitis. The older classification of genital tuberculosis and renal tuberculosis is not entirely correct for the two are more often associated than not. The finding of a tuberculous epididymis should call for a thorough search for other foci of infection in the individual for it is probable that tuberculosis of the epididymis is never primary.

Prostatic tuberculosis occurred in 2 cases. In one, a man of 64, the symptoms were mistaken for prostatism. The prostate was resected and the pathologist reported tuberculosis. Search was then made of the upper urinary tract and in the right kidney was found the apparent primary lesion. A right nephrectomy was done and the patient made a good recovery and lived comfortably for 12 years thereafter.

The other case was in a man of 21 years who had bilateral renal tuberculosis with symptoms of obstruction at the vesical neck. Cystoscopic study showed an obstruction to be present in the prostatic area. This was resected and proved to be a tuberculoma occupying the position of a prostatic middle lobe.

Calcified lymph nodes were found in only 2 cases. The percentage of 6.1 is only one-half that of Cristol and Greene of Rochester, Minnesota, who found in their series 13 per cent calcified lymph nodes.

Hunner's ulcer was a surprise finding in 3 of our cases. One who is not completely familiar with the bladder picture of tuberculosis might venture the criticism that the lesions resemble each other. However, such is not the case. The Hunner's ulcer appeared after the bladder mucosa had cleared of the tuberculous infection and was so typical in every way as to be unmistakable. Fulguration

MORTALITY AND SURVIVAL

Six are known to be dead. They lived an average of 7.1 years after nephrectomy. Fifteen are known to be living at this time. These have survived an average of 14.2 years. Nine are as yet unaccounted for.

DESCRIPTION OF FOUR CASES

Case 1. R. K., a 39 year old male whose occupation was railroad agent in a small town, was first seen December 26, 1925. He complained of being very tired all the time, of soreness in his abdomen, and a sharp stabbing pain in his right upper quadrant. These symptoms began 1 year previously. In May 1925, he began to have frequent and painful urination. By September 1925, he began to notice that at times his urine was bloody. A few weeks later he passed a large quantity of blood and clots. He had lost 20 pounds in weight during the past 6 months.

Examination of the urine showed it to be loaded with pus. A few blood cells were present. X-ray of the chest showed healed tuberculosis. Cystoscopy and pyelogram showed both kidneys damaged, the right worse than the left.

On January 23, 1926, a right nephrectomy was done. The pedicle case was found to be thrombosed and a typical autonephrectomy was found.

The patient made a good recovery from his operation although he formed some draining sinuses at the site of the wound. He was dismissed from the hospital March 6, 1926 and returned to work April 1 of that year. He felt much better. Voided urine examined after nephrectomy showed many acid fast bacilli, even in the freshly voided uncentrifuged specimen. I examined this patient at intervals of 3 months for a good many years. He always showed tubercle bacilli in his urine.

In 1938 he went to the Hertzler Clinic at Halstead, Kansas, and was seen by Dr. Chesky who wrote me to ask if I had removed a tuberculous kidney on the patient. He had worked steadily all those years. He was known to be alive and still on his job in 1940. Since then we have been unable to trace him.

Here is a patient who, by all the rules, should have been dead in 1929. He lived a total of 15 years and was never invalided to the extent that he could not carry on his work.

Case 2. P. F., a white male aged 21, was first seen July 31, 1937. His main complaints were burning and frequency of urination. These complaints began early in 1936. His urine showed a marked amount of pus. Cystoscopy showed a typical tuberculous bladder with a large tuberculoma almost blocking the vesical outlet in much the same manner in which a middle lobe of the prostate produces obstruction in older males. Before catheters could be passed to the kidneys and the ureters seen, this tuberculoma had to be resected. Pyelograms showed bilateral renal tuberculosis with tubercle bacilli found in the urine from both kidneys. X-rays of the chest showed what the roentgenologist called tuberculosis; later observation caused him to change to a possible histoplasmosis. This latter, I believe, cannot be correct for the patient has outlived that diagnosis.

He was one of the first patients to be given sulfa compounds. The secondary infection was markedly improved by this means. One per cent phenol solution injected into the bladder caused a marked improvement and the tuberculoma did not return. He went back to work after 2 months in the hospital.

In January 1938, he had an attack of chills and fever. His blood pressure was 96/63 and has remained at that level. He began to have pain in his right side; a hydronephrosis of 150 cc developed. It was necessary, about every 2 or 3 months, to pass a ureteral catheter into the right kidney and relieve the pressure of the hydronephrosis. He was thus relieved of pain and remained fairly comfortable until October 1942, when he had another attack of chills and fever and pain over the right kidney. This was relieved by passage of a ureteral catheter. He spent some time in the hospital in July 1944. In July 1945 he complained of a pain in his right lower abdomen. An x-ray taken then showed a very large stone in the right lower ureter. The stone was fusiform in shape, 11 cm. in length and 3 cm. in diameter at its greatest circumference. It was removed by a right rectus incision. The incision healed promptly and by primary union.

The patient is still getting along quite well. He is able to work every day. He was married 3 years ago. In July 1946 a left epididymitis developed which was evidently not tuberculosis because it subsided under ordinary treatment.

By all the rules, this man should have been dead in 1940; he is still very much alive.

Case 3. S. W., a white married woman of 34 years, who had already borne 6 sons, was first seen by me in April of 1924. Her symptoms were nervousness, pain in her left side and back, and headache. When first seen she had had a 7 months premature delivery in 1921. Following that she had a stone removed from the right kidney. She did not do well; so, 6 months later her right kidney was removed. She got along fairly well until late in 1923 when she began to have constant pain in her left kidney coupled with marked dysuria. At the time she was seen by me, she was in the hands of a competent internist who called me to solve the anuria which had apparently developed. Events proved that she was faking an anuria because of her then hysterical state. At this time, flat ulcerative patches were observed in her bladder and the Mycobacterium tuberculosis was found in the catheterized urine in abundance. The acid fast bacilli were also found by ureter catheter from the left, or remaining, kidney. This kidney was found to have a hydronephrosis at that time (1924) of 30 cc. The ureter was also the seat of many strictures which were undoubtedly tuberculous in origin. About twice a year up until 1943, the patient would have episodes of acute obstruction to the remaining kidney. This was accompanied by great pain in her left upper quadrant and severe headache. It could be relieved only by passing a ureteral catheter to the kidney and drawing off the accumulated contents of the hydronephrotic sac.

Within a period of 5 years, or by 1929, the flat tuberculous ulcers had disappeared from her bladder and acid fast bacilli could no longer be found in her urine. Her blood pressure was 110/80.

In 1939 she came in with a very severe attack, during which she was vomiting;

her nonprotein nitrogen rose rapidly to 200 and she became comatose. It seemed like the finish, particularly as I was unable to pass a catheter to her kidney. I finally succeeded in passing a fine olive-tipped whalebone bougie to the kidney. Over this I slipped a No. 7 ureteral catheter with the tip cut off. She had 150 cc of urine in the renal pelvis and the catheter was left in place. The kidney started to secrete and within 24 hours she was out of danger. The catheter was withdrawn from the ureter in 48 hours and the kidney continued to secrete normally. She was dismissed at the end of a week.

There have been only two episodes since that time, both of a milder nature. She was last seen by me in the summer of 1946 at which time she appeared quite well. Within the past few days I read a letter from her in which she states that she does not feel very well.

According to all the rules the patient should have been dead in 1927 because she had acid fast bacilli from her remaining kidney following nephrectomy. This year she will be 57 years of age. The observation period, therefore, has been a span of 26 years. She passed through all this without the aid of the sulfa compounds or the antibiotics.

Case 4. T. M. P., a white female, at the age of 14 years was first seen by another urologist in 1933. The onset of her trouble had been 6 months before that time. Pyelograms showed bilateral involvement, equally severe on both sides. Acid fast bacilli were found and guinea pig inoculation was positive. Five years later, in 1938, she was brought to me. At that time she was quite ill. She had frequency of urination associated with fever. She also had nocturia of every 30 minutes. Acid fast bacilli were found in the urine. Her blood pressure was 120/80. Cystoscopy was done but no catheters were passed to the kidney. The bladder was studded with tubercles. Excretory pyelograms beautifully portrayed the urinary tract. Comparing these intravenous films with the retrograde pyelograms of 1933, it was evident that the right kidney had improved somewhat but there was a large abscess in the lower pole of the left. Since there seemed to be nothing to lose and everything to gain by removal of the abscessed kidney, this was advised. Accordingly on January 5, 1938, her left kidney was removed. The operation was accomplished without spilling any of the contents of the kidney or the abscess. The ureter, strange to say, looked quite normal, both in size and appearance; so, only one-half of its length was removed.

She made an excellent recovery and was fever free in a few days. No sinuses developed at the site of the wound. She was put on a regimen of rest, sunshine, vitamins, plenty of good food and sulfacetamide. In 18 months the acid fast bacilli no longer could be found in her urine and the guinea pigs survived. The tuberculous lesions in her bladder disappeared and she had no dysuria and could sleep all night without ever once arising to urinate.

Then early in 1941, she came to me stating that she wanted to get married. I advised against it and so did her parents, but on May 17, 1941, she was married. On May 22, 1943, she was delivered of a baby. She seemed to be completely cured. Her urine remained clear.

Early in 1946 she again became pregnant and this time, on August 1 of the same year, she produced a seven months premature baby after a stormy time. The child died 3 days after birth and had a patent ductus arteriosus. The patient went into a decline, all her old symptoms flared up and acid fast bacilli were again found in her urine. She was put to bed and streptomycin in doses of 3 gm. per day was given her for nearly 3 weeks, or a total of 60 gm. Since the completion of this treatment in October 1946, she is free of all symptoms and repeated search for acid fast bacilli in her urine has been negative and the guinea pig still lives.

Here is a patient who has been followed for 14 years and has borne 2 children. By all the rules, she should have died in 1941; she is alive and quite well today.

STREPTOMYCIN

Five cases have been treated with streptomycin with encouraging results. I cannot give all the details of the treatment here but will do so in another place. When only 1 gm. or 1,000,000 units of streptomycin is given per day, the results are not as good as when 3 gm. per day are given. It is much better to give 60 gm. over a 20 day period than over a 60 day period. Much larger doses probably should be given.

CONCLUSIONS

Renal tuberculosis is generally considered to be a grave threat to life. Bilateral renal tuberculosis is, if possible, a double threat. *If nothing else, this study has taught us that until the patient with renal tuberculosis is actually dead, one should not give up hope nor fail to plan new methods of treatment.* Practically all of the cases reviewed here were treated before the days of the sulfa compounds and the antibiotics. As soon as streptomycin gets cheap enough to be more widely used, we believe we can look for still better results when this substance is used following nephrectomy.

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THE USE OF ESTROGENS IN THE TREATMENT OF BLADDER TUMORS[1]

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It is not our intention to present a new therapeutic approach to vesical neoplasm, but to present our observations on the use of estrogens as an adjunct in the control or treatment of vesical tumors. Our presentation does not represent a complete study, but merely our early observations, a brief review of our cases and in addition a compilation of the existing literature.

Our early work was initiated by one of us (O.G.) who reasoned that since both the bladder and prostate were of similar embryologic origin, the estrogenic response seen in prostatic neoplasm might well be experienced in vesical malignancy. It was with this in mind that the first patient was treated. He was rapidly approaching the terminal stages of vesical neoplasm and when he refused further surgery stilbestrol was initiated. The patient continued not only to live, but experienced subjective improvement to a degree that he was able to resume his occupation. He has now continued in apparent health for more than 3 years, although on cystoscopic examination, the neoplasm seems little altered. The tenesmus and frequency have improved.

It was with the stimulation of this first instance of apparent palliative success that we launched our study and undertook an intensive search of the literature. The literature in reference to estrogenic therapy of bladder cancer was scant, but the theories to explain the means by which estrogens or substances with estrogenic properties might affect tumor growth were numerous.

To review the embryology of the bladder and prostate briefly it may be pointed out that as the hind-gut gives rise to the allantois this structure finally separates from the hind-gut and a dilatation in its midportion forms the bladder. The constriction of the inferior portion of the bladder which accepts the wolffian duct is the eventual posterior urethra and it is out-pocketings from this area which give rise to the prostate. It is then readily seen that the bladder and prostate are of similar origin. It would seem then, that estrogens might be equally effective in rectal, vesical and prostatic carcinoma. Haddow and his associates found that a substance with estrogenic properties (triphenylchlorethylene) was not effective in rectal adenocarcinoma although they report but a single case. In our own experience a patient with primary rectal neoplasm has obtained relief from stilbestrol, 10 mg. daily, in spite of the fact that the neoplasm has not been altered in size, although it would seem there is a suggestion that this substance has diminished the growth rate.

Tadros, working in Cairo, is of the opinion that synthetic estrogens are distinctly antitumorigenic and not carcinogenic in humans. Badger and his associates investigated numerous compounds to discern the presence or absence of non specific cellular toxicity to explain growth inhibitory properties They concluded that it was not a toxic factor since such drugs reveal no estrogenic properties and do not influence tumor growth On the other hand, estrogenic substances exhibit growth inhibitory properties and are non toxic

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[1] Read at annual meeting, Southeastern Section, American Urological Association, Palm Beach, Fla., March 27, 1947.

Zondek suggested that the effects of estrogen on tumor growth were by virtue of the anterior pituitary This theory was further suggested by Haddow and Robinson in reference to certain carcinogenic compounds These authors felt that there was in addition a certain amount of local action necessary as well Noble agreed too with the factor of antuitary suppression but championed the belief of local depression of cellular metabolism The exact mechanism has obviously eluded present observation, but it may be said that its existence is not mythical since the inhibitory power has been measured quite accurately in experimental animals Salter and Nathanson have shown furthermore, that breast tumor transplants do not grow readily in animals previously given stilbestrol It may be that the hormone may affect the nutrition of the tumor through some activity on the vascular stalk, this possibility was suggested by Barnes It may be concluded that compounds having estrogenic properties depress tumor growth, but the modus operandi is not clear

In our review of the literature it was found that Haddow, Watkinson and Paterson, working in the Royal Cancer Hospital of London, were apparently the first to employ a substance with estrogenic properties in the treatment of a bladder tumor These authors subjected their patient with vesical neoplasm to triphenylchlorethylene on February 18, 1941 This substance was used because of its comparative prolonged action due to its insolubility in body fluids

The patient whom they report was a man of 71 who had suffered metastasis of his vesical carcinoma to the tenth dorsal vertebra After the exhibition of triphenylchlorethylene there was rapid improvement in this patient's general condition, 2 months later there was marked improvement of the local condition and finally almost complete regression of the primary tumor The squamous cells had undergone practically complete necrosis according to the histological report This finding is strikingly similar to our findings with the use of stilbestrol The patient died some 11 months following the initiation of this treatment of circulatory failure and it is interesting to find at the necropsy that no bladder tumor was discernible, but viable malignant cells were found in the bladder wall upon histological study

Haines and Mirch (1943), reported on 10 instances of bladder tumor treated with estrogenic substance, 7 of these patients being males and 3 females This is the largest group reported in the literature In the 3 women the authors felt there was no relief and possibly the estrogenic therapy accentuated the symptoms Among the men in all but one there was a variable degree of improvement In an individual with grade 2 infiltrating carcinoma the symptoms were controlled and an increase in the bladder capacity was noted A urethral papilloma disappeared following estrogenic therapy and this same experience was duplicated in a sessile tumor immediately behind the sphincter, but following

TABLE 1

PATIENT	AGE	TUMOR SITE	HISTOLOGICAL DIAGNOSIS	REMARKS
1. T. J. Mc.	76	Sphincteric margin, left	Papillary carcinoma with spread to prostate grade 4	Stilbestrol, total 500 mg. with no apparent effect on course of disease. Pulmonary metastasis and death within 3 years of initial symptoms.
2. P. S.	72	Left lateral wall and sphincteric margin	Adenocarcinoma, grade 4	Transurethral resection followed by 400 mg. stilbestrol in 3 months. No change in tumor size and no symptomatic relief. 4 months later, following radium and 650 mg. stilbestrol, only a single residual nodule. Moderate symptomatic improvement.
3. J. W. B.	38	Near ureteral orifice, two small tumors	Papillary carcinoma, grade 1 or 3	Fulguration followed by 348 mg. stilbestrol in 5 months. At this time a minimal recurrence which was fulgurated and patient maintained on 15 mg. stilbestrol per week since that time. No recurrence in past 4 months.
4. T. K.	57	Generalized papillomatosis. Large tumor near right ureteral orifice	Papillomata, papillary carcinoma, grade 3	Fulguration of tumor 2 years previously. Returned with generalized papillomatosis disappeared after 2 months with a total of 290 mg. stilbestrol. Partial resection of bladder to remove large tumor. A year later a recurrence of the sessile tumor which was treated with radium and no recurrence in past year.
5. H. O. M.	72	Generalized papillomatosis Sphincteric margin, left	Papillomata Papillary carcinoma, grade 2	11 months after first tumor was fulgurated, there developed a generalized papillomatosis with marked hematuria resulting in a severe anemia. 48 days later after 800 mg. of stilbestrol there were 4 residual tumors. 7½ months later only 3 remaining tumors. These tumors were treated with radium.
6. A. B.	53	Sphincteric margin, left	Papillary carcinoma, grade 3	During 3 year period the tumor recurred after fulguration on two occasions. Stilbestrol (200 mg.) diminished frequency, urgency and tenesmus, but no gross change in tumor size. Partial resection of bladder with continuation of stilbestrol and no evidence of recurrence in past 4½ months.
7. J. C.	41	Sphincteric margin and lateral bladder wall, right	Squamous cell carcinoma with extension into bladder wall	After more than 300 mg. stilbestrol, no symptomatic relief and no change in gross appearance of tumor. Treated with radium, but patient has not been seen since that time, some 5 months ago.
8. A. B.	56	Lateral wall right and entire base	Papillary carcinoma, grade 4	Recurrence of bladder tumor seemed very rapidly growing. Patient refused further surgery and stilbestrol given in 5 mg. daily dosage with marked symptomatic relief. Patient still in apparent health 3 years later, tumor growth has not diminished, but seems rather stationary in its progress.
9. O. B.	59	Small tumor right ureteral opening	Papilloma	Biopsy taken with resectoscope and base fulgurated. No recurrence in past 8 months and patient is being maintained on stilbestrol 15 mg. per week.

TABLE 1—*Concluded*

PATIENT	AGE	TUMOR SITE	HISTOLOGICAL DIAGNOSIS	REMARKS
10 B L	79	Small tumor mid *trigone*	Early transitional *carcinoma*	Biopsy taken and another after 140 mg stilbestrol *The tumor was greatly reduced on* second observation Patient died some 2 months later and necropsy refused
11 E J C	64	Small tumor ureteral orifice left	Early transitional carcinoma	Tumor fulgurated and patient retained on stilbestrol 20 mg per week 14 months later a very small area suggesting recurrence which was biopsied and fulgurated Patient has not been seen since this last procedure of 3 months ago

discontinuation of therapy there was a recurrence above the left ureteral orifice In another instance the authors felt that they relieved vesical spasm In short, these authors believed that there was improvement of at least palliative proportions in 6 out of 7 males and that the treatment was without benefit in the 3 women

In 1945, Shivers reported 2 cases of vesical neoplasm which were treated by bilateral subcapsular orchiectomy The first case was apparently benefited both by a reduction in the tumor activity and by general feeling of well being with a distinct disappearance of urinary discomfort during a 3 year period

The second patient had been followed for a very short time, but his urinary complaints were greatly minimized immediately following orchiectomy. These reports remind one much of the findings in prostatic carcinoma

Prostatic and vesical neoplasm present cytologic similarities Prostatic carcinoma is characterized by cellular irregularity in size and shape which demonstrate the loss of the palisade arrangement and irregular nuclei in both contour and staining reaction In the event that the process is well advanced the acini may be filled with neoplastic cells so that the underlying connective tissue may virtually be obliterated A similar picture is present in vesical neoplasm which reveals the variable cellular morphology and nuclear abnormality with compression and infiltration of the tumor cells into the stalk of the vesical neoplasm which is composed of adult connective tissue derived directly from the bladder.

The picture of vesical and prostatic new growth following stilbestrol therapy is virtually identical. The cytoplasm is markedly vacuolated and the nuclei reveal an irregularity in staining reaction, reduction in size, and are often pyknotic and eccentrically placed in the cell In many areas cellular debris is our only evidence of the previous existence of a cell The cytologic picture in prostatic carcinoma following stilbestrol has been adequately described by many authors: Schenken, Bruns and Kahle, Heckel and Kretschmer, Wattenberg and Rose, and others, but the effects of stilbestrol on bladder tumors have not, to our knowledge, been previously described

We will see that stilbestrol has at least afforded comfort to a few of our cases of vesical neoplasm and though our series is small and not of statistical importance we hope this report will stimulate others toward its use and thus lead to an early and just evaluation.

Our 11 cases are summarized in table 1 which includes the significant pre- and postoperative findings. The amount of stilbestrol used routinely was 5 mg. daily and exceptions to this dosage will be recorded in the table.

In summary of our findings we find that the most consistent effect of stilbestrol is the symptomatic reduction of vesical irritability. Stilbestrol afforded subjective relief in 9 of the 11 cases reported. Tumors of grade 3 and 4, though showing histological change due to stilbestrol, were practically unaltered clinically. Papillomata consistently disappeared under estrogen therapy. In 2 instances multiple papillomata were destroyed and thus virtually insoluble situations of neoplasm were transformed into a soluble problem. Further study and a greater series is needed to clarify the therapeutic position of estrogens in vesical neoplasm.

SUMMARY

Eleven instances of vesical neoplasm are reported along with their response to stilbestrol therapy. The most consistent effects were subjective relief and dissolution of papillomata.

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SUPRAPUBIC SUCTION VESICAL DRAINAGE: A NEW APPLIANCE[1]

FRANK J. PYLE AND ROBERT P. HENDERSON

The pendulum swings, suprapubic vesical operations for calculi, tumors, diverticula, adenoma of the prostate, impassable urethral strictures, injuries to the urethra and spinal cord injuries have been and always will be necessary in many cases. With the increase in the popularity of transurethral resections of adenomatous growths of the prostate and of papillomas of the bladder, there has been a decrease in the number of cystostomies. On the other hand, with an increase in the number of well trained urologists, the total number of vesical operations approached suprapubically has increased. It is my belief that the majority wish to follow these operations with suprapubic drainage but may encounter difficulty in obtaining "per primam" healing of the incision.

Anyone with good surgical training should be able to perform a suprapubic cystostomy. For improvements in the surgical technique in performing suprapubic cystostomies one should refer to excellent papers such as that by Hamm in which he stresses the importance of the correct placement of the tube, and one by the late Henry Morton where he stresses the importance of incising the prevesical fascia transversely avoiding the space of Retzius.

One year ago Deming discussed bladder drainage and stated. "There is no foolproof apparatus, and the more complicated is an appliance the more care it needs." Many suction appliances have been advised and have proved very successful in improved wound healing and the prevention of urine leakage, but the majority are complicated. Harold Stedman adopted a motor suction pump for bladder drainage and when available it offers one of the most convenient methods we have found. Bandler, Fish, McCrea, and others have devised models for suprapubic suction drainage. All of these have given good results but necessitate the purchase of special appliances and the one desired is not always available in the hospital when the surgeon wishes to use it. This is especially true when you are called to a general hospital where you only work occasionally.

The type of suction I am presenting involves one new principle, and that is the suction is applied to the outer or larger tube and the smaller tube acts as an air intake preventing bladder collapse and suction of bladder mucosa into the tubing. When first used, suction was applied to the smaller tubing but this became obstructed by clots, debris, etc., and proved a marked disadvantage.

This new appliance makes use of materials found in almost all hospitals (fig. 1). We have a suprapubic tube of the Malecot 4 wing type No. 34. A Pezzar catheter works as well although enlarging the openings is advisable. A larger size than No. 34 may be used but a smaller size has given trouble. The inner or air tube is a No. 12 soft rubber catheter with one or more extra eyes cut near the end. The third piece is a glass Y tube of sufficient size for drainage and to allow for the application of the rubber tip. We use the large perforated rubber tip from a cystoscope. We have used the tip from one end of a sterilized intravenous tubing set and on one occasion used one from a medicine dropper and found it as satisfactory. For the mechanical suction we have used both a Stedman electric suction pump and a Chapman water suction pump. The former is preferred because of convenience but the latter works as well.

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[1] Read at annual meeting, Southeastern Section, American Urological Association, Palm Beach, Fla., March 28, 1947.

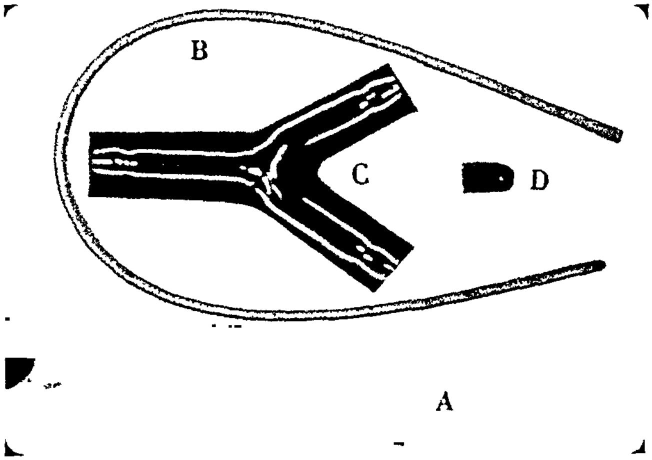

FIG. 1

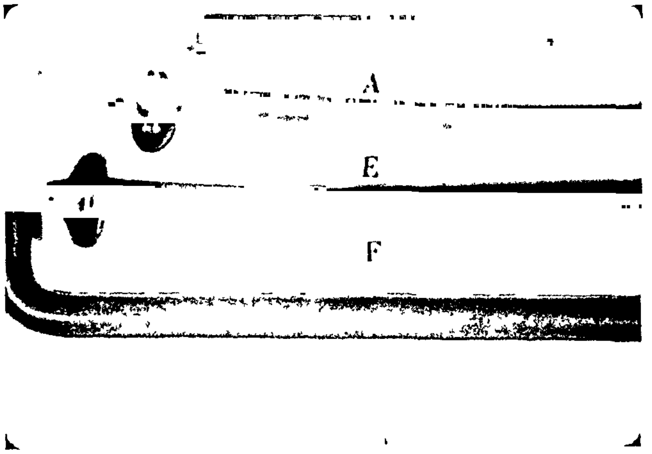

FIG. 2

Figure 2 shows 3 types of suprapubic tubes that may be used. The third or whistle tip angulated drain as well as the Freyer tube may be preferred by some for ease in removing. If this type is used one must measure the distance from the bladder end to the point of cutting very carefully, and mark this off on the inner air-intake tube. From this point on, assembling is the same.

In figure 3 we have the apparatus assembled. The drainage tube has been cut and the removed portion attached to one end of the Y tube. The portion A will be the only section in the bladder at the end of the operation. The No.

12 soft rubber catheter B is first drawn through the rubber tip D and then passed through the glass Y tube until the distal end reaches the bulb of the Malecot drain.

Figure 4 is a section drawing showing the appliance in relation to the bladder. At the completion of the cystostomy we would have only the Malecot or Pezzar drain A in place. The remaining portion including B, C, and D, assembled is introduced into the drain. Suction is applied using a suction tube, collection bottle, and either a Stedman electric or Chapman water suction pump. After starting the pump, check the negative pressure by clamping tube B then releasing. If working correctly, air will be heard entering the smaller tube. Another check is to introduce normal saline solution into the air intake tube B and if correct the solution will be immediately drawn out of the bladder into the reception bottle. If desired a small section of gauze may be tied over the end

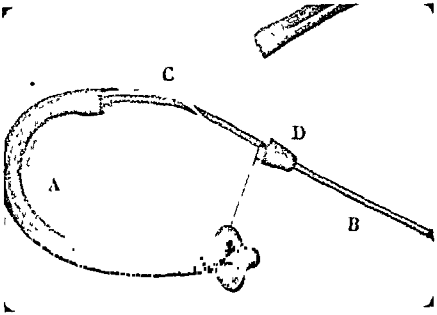

Fig. 3

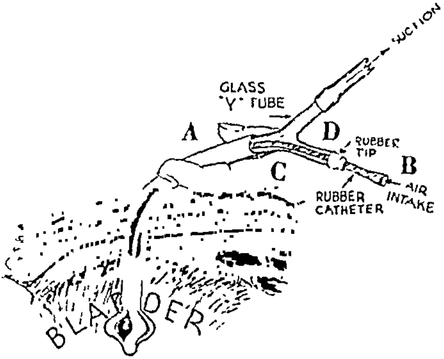

Fig. 4

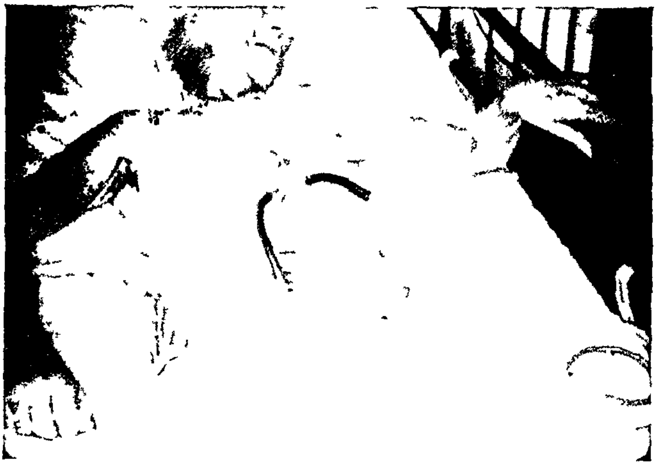

Fig 5

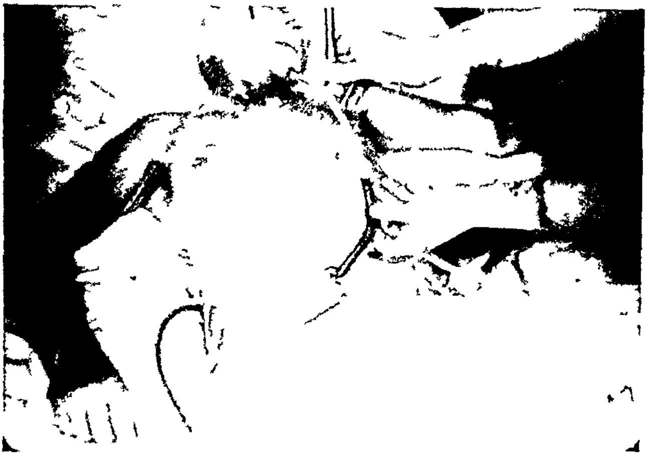

Fig 6

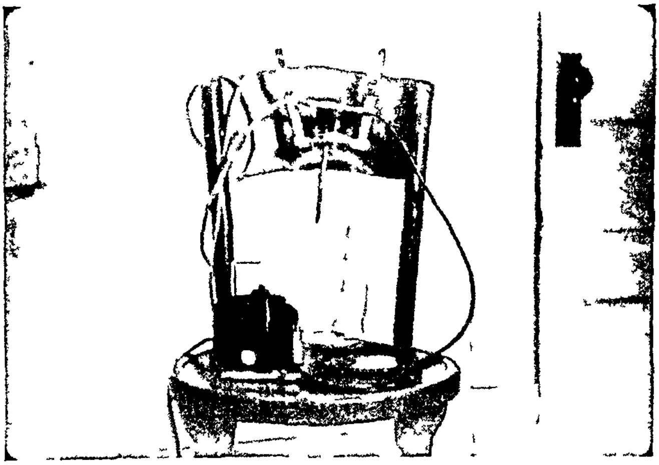

Fig 7

of tube B but this has not been necessary. Air borne organisms will enter through the gauze although it appears more aseptic.

Figures 5 and 6 are photographs of this suction apparatus in operation. In figure 5 the suction tube running from the patient is connected to a receptacle or jug fitted with air tight connections which in turn runs to a Stedman pump or a Chapman water suction pump as illustrated in figures 6 and 7. Figure 6 illustrates the ease with which the apparatus may be removed from the large suprapubic suction tube for cleansing.

If at any time the apparatus fails to function, becoming obstructed from debris, the assembled portion may be removed from tube A, the bladder irrigated through this large tube and the parts washed, resterilized, and easily assembled. After healing has taken place which is usually in 4 to 6 days, we can convert this into straight suprapubic vesical drainage by removing all except tube A as described above.

This apparatus may be used for kidney suction drainage, setting it up with smaller sized tubing. We have not tried this in kidney cases and are not able to conclude any advantages over the regular method. I intend using it in cases where constant irrigation with normal saline or other solution is desired. Here we will use a urethral catheter in the upper pole and apply this suction apparatus to the lower calyces using a No. 20 or No. 22 Malecot catheter. Deming has described a very satisfactory method of kidney irrigation, although he does not use suction on the lower pole drain. So far we have not found kidney suction drainage necessary.

CONCLUSIONS

A simplified, easily convertible appliance for vesical suction drainage has been described. The application of suction to the large tube is a new principle.

Its use for drainage elsewhere, as following kidney operations, is suggested, but so far has not been indicated.

This apparatus has been used in all of our suprapubic cystostomies over the past 3 years and has proved very practical and successful, the patients remaining dry and the incisions healing rapidly.

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PERSISTENT CLOACA IN THE FEMALE: REPORT OF TWO CASES CORRECTED BY OPERATION[1, 2]

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Persistent cloaca in the human is probably the rarest of all rare developmental defects. It therefore seems advisable for the author to report in some detail 2 cases which have been corrected by operation.

A careful search of the literature since these patients were operated upon revealed reports of only 5 other cases treated surgically. Four were instances of imperforate anus with the rectum opening into the vagina through the posterior wall or at the posterior fourchet; the fifth, in a male, was a case of imperforate anus with the bowel connecting with the deep urethra, which opened in the perineum behind a hypospadic penis.

In the author's cases, the plight of the patients, both of whom were young females, was heartrending. They were completely ostracized from their fellows and unpleasant to their families by reason of the stench which accompanied their condition. Normal friendships and activities were denied them. Both attempted to attend school at the usual age, but the ridicule and cruel remarks of their classmates drove them out in a single day. This resulted in these children becoming recluses, and their dejection was pitiful. A "hang-dog" expression, irritability, and fear marked them. Upon entrance to the hospital, neither could read or write although one was 9 and the other 7 years of age.

When repair was accomplished, both of these little girls blossomed out into a new world, which changed their dispositions and even their looks.

NATURE OF THE ANOMALY IN AUTHOR'S CASES

In view of the fact that the human embryo passes through a period during which, like birds and reptiles, it has a common cloaca for both feces and urine excretion, it is a little strange that persistent cloaca is not observed more often. The cases described here were true cloacas in the sense that feces and urine emptied into a cloacal type of pouch and emanated from this pouch through the same aperture.

In the first case, both ureters emptied into a continent bladder, but there was overflow incontinence as the bladder was absolutely untrained and without sensation. The rectum opened into the vestibule of the vagina (cloacal pouch). Feces passed constantly and the excretions were mixed in the vaginal vestibule which was completely covered at birth and was opened by the obstetrician with two stab wounds, through which urine and feces exuded (fig. 1).

In the other case, the rectum opened into the lower part of the vaginal vestibule and was continent; but the ureter from the patient's single (right) kidney

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was aberrant, opening in the upper wall of the vagina, and was incontinent, hence she was wet constantly (fig 6)

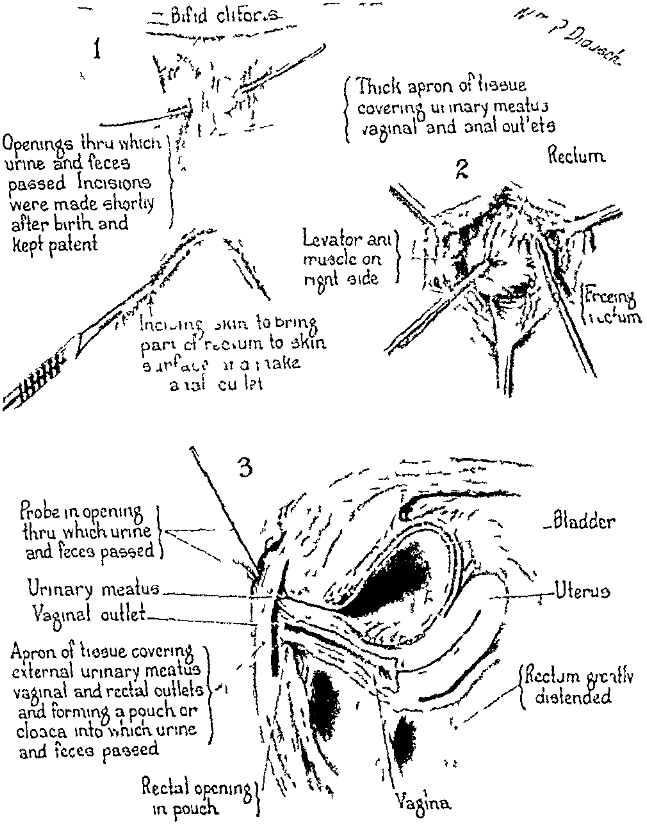
Bifid clitoris
1
Wm P Didusch
Thick apron of tissue covering urinary meatus vaginal and anal outlets
Openings thru which urine and feces passed Incisions were made shortly after birth and kept patent
Incising skin to bring part of rectum to skin surface and to make anal outlet
2
Rectum
Levator ani muscle on right side
Freeing rectum
3
Probe in opening thru which urine and feces passed
Urinary meatus
Vaginal outlet
Apron of tissue covering external urinary meatus vaginal and rectal outlets and forming a pouch or cloaca into which urine and feces passed
Bladder
Uterus
Rectum greatly distended
Rectal opening in pouch
Vagina

Fig 1 Case 1 Congenital abnormality in 9 year old female, operative restoration Rectum opened into vaginal vestibule (cloacal pouch) which was covered at birth by an apron of tissue and was opened by obstetrician with two stabwounds, through which urine and feces passed *1*, Condition present, apron of tissue covers urethral, vaginal and rectal outlets Skin incision to expose portion of rectum and make new anus *2*, Freeing rectum *3* Sagittal view of condition present

In females, the ectopic orifice of an aberrant ureter is generally located in the urethra or vestibule, but there are reports of its also having been found in the vagina or uterus. Hepburn questions the validity of the latter findings. He points out that the ureter arises from the wolffian system, and the vagina and uterus from the müllerian structures, and he believes an anastomosis to be impossible. However, Winterton explains that such findings are due to perforation of a wall between the müllerian and wolffian structures.

In none of the 5 other cases since found in the literature was the fecal anomaly complicated by the element of urinary incontinence present in both of the cases described here.

REPORTS OF TWO CASES

Case 1. M. P., a nine year old white female, was admitted to the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital on June 14, 1938 with a history of congenital deformity of the genitalia. She had had an appendectomy and a colostomy previously, and had been referred to the author for further study as to the restoration of her genital tract.

Physical examination showed some tenderness to deep palpation in the region of the lower poles of both kidneys. The pubes were separated 7 cm. and immediately over this area was a fluctuant mass which was evidently the bladder. The recti muscles were separated. Examination of the genitalia revealed bifid clitoris and wide separation of the labia majora due to separation of the pubes. There was no evidence of a vaginal, anal, or urethral opening. Just below the normal location for a urethral orifice, on each side, was a fistulous tract from which feces and urine exuded.

Urinalysis showed 6 to 8 red blood cells, 5 to 10 white blood cells, and numerous epithelial cells; otherwise the laboratory findings were essentially negative.

The patient was studied intensively before any operative procedures were suggested. (See figure 5.) Excretory urograms showed a normal upper urinary tract but the pictures failed to show the location of the distal end of the ureters. Observation cystoscopy was done on several occasions and retrograde pyelography was attempted. The ureteral orifices were not located, and it was finally concluded that the cystoscope, inserted through the lateral fistulous tracts, entered the uterine cavity and not the bladder. It was also believed that the fecal material entered the cloaca in the midline at its posterior part, near the skin edge.

X-ray examination of the gastro-intestinal tract showed a vertical stomach of medium size with normal peristalsis and no defects. There was a tremendous dilatation of what appeared to be the rectum. X-ray of the pelvis showed marked spina bifida.

After these studies, it was known that the patient had a normal urinary tract, but it was not known where the ureters entered. It was decided first to make a perineal incision to see if she had any sphincter fibers, with the idea of creating an artificial anus.

On July 13 (1 month after admission) a plastic operation was done, creating an artificial anus. A loop of the rectum was pulled through an incision in the perineum and sutured so that it protruded outside (figs. 1 and 2). Five days

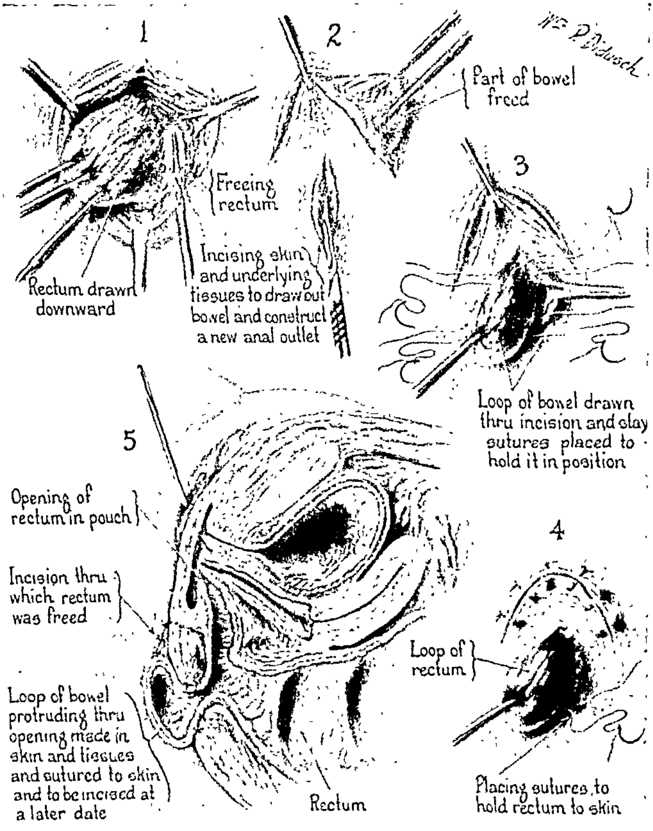
1
2
3
4
5
W. P. Didusch
Part of bowel freed
Freeing rectum
Rectum drawn downward
Incising skin and underlying tissues to draw out bowel and construct a new anal outlet
Loop of bowel drawn thru incision and stay sutures placed to hold it in position
Opening of rectum in pouch
Incision thru which rectum was freed
Loop of rectum
Loop of bowel protruding thru opening made in skin and tissues and sutured to skin and to be incised at a later date
Rectum
Placing sutures to hold rectum to skin

Fig. 2. Case 1. Construction of artificial anus. *1*, Freeing rectum. *2*, Perineal incision to draw out rectum and construct new anus. *3*, *4*, Loop of rectum drawn through incision and sutured to hold it in position. *5*, Sagittal view showing condition after operation. (Five days later, protruding loop of rectum opened with coagulating current and catheter inserted through opening.)

later this protruding distal loop of the rectum was opened with a coagulating current and a catheter inserted through the opening. For 2 weeks this artificial rectum was irrigated daily.

The patient was then taken to the operating room, an exploratory operation done, and the lateral fistulas and rectal entrance into the cloaca closed. The cloacal pouch was exposed by dividing the apron of tissue by an incision from one fistulous opening to the other (fig. 3, *1*). Examination revealed a cervix in its upper portion. Lower, at the anterior midline near the skin margin, was a urethral opening of fairly normal appearance. A sound passed into this entered the bladder, releasing urine. The rectal opening was found next to the skin margins of the cloaca, in the midline, and was about $\frac{3}{4}$-inch in diameter (fig.

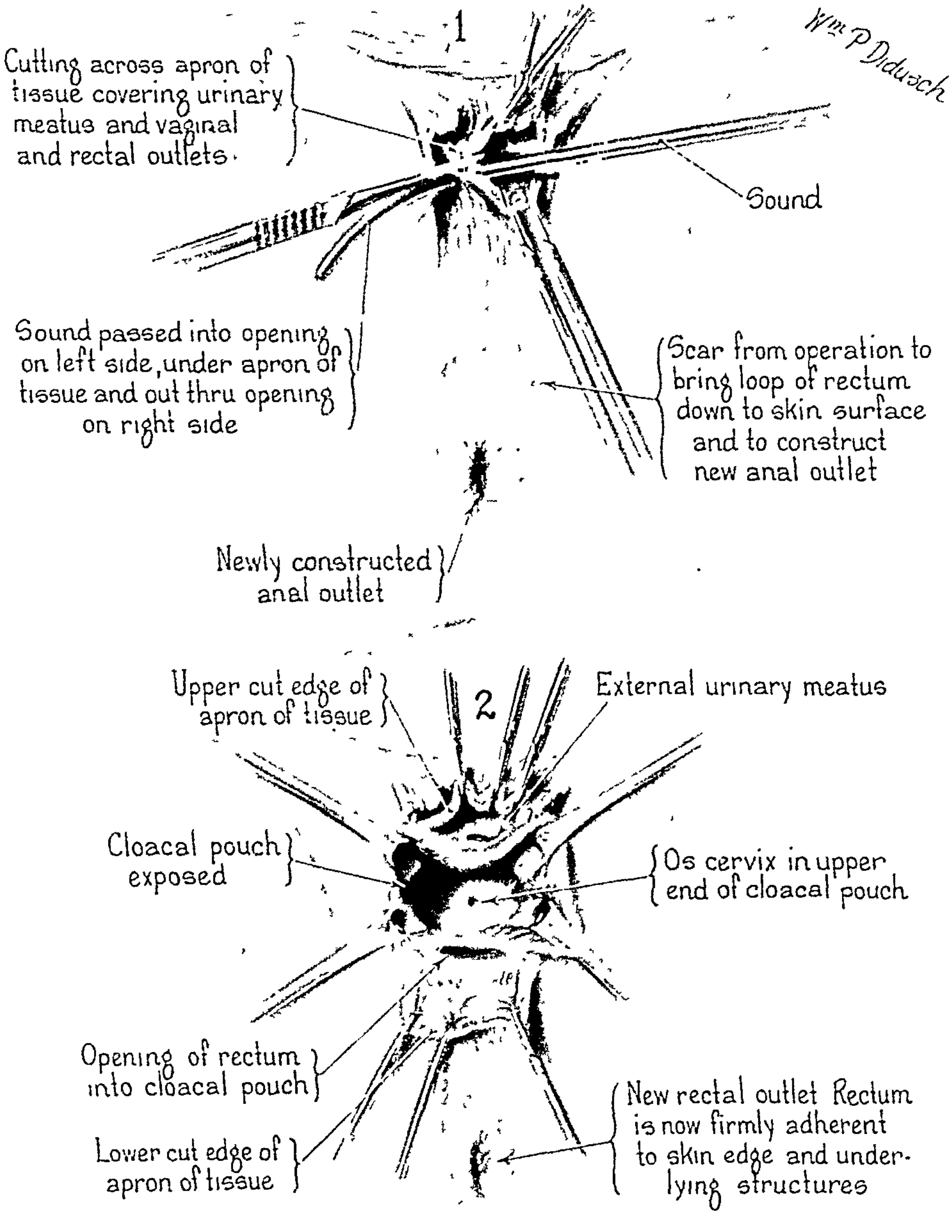
1
Wm P Didusch
Cutting across apron of tissue covering urinary meatus and vaginal and rectal outlets.
Sound
Sound passed into opening on left side, under apron of tissue and out thru opening on right side
Scar from operation to bring loop of rectum down to skin surface and to construct new anal outlet
Newly constructed anal outlet
2
Upper cut edge of apron of tissue
External urinary meatus
Cloacal pouch exposed
Os cervix in upper end of cloacal pouch
Opening of rectum into cloacal pouch
Lower cut edge of apron of tissue
New rectal outlet Rectum is now firmly adherent to skin edge and underlying structures

FIG. 3. Case 1. Closure of lateral fistulas and rectal entrance into cloaca. *1*, Exposing cloacal pouch by dividing apron of tissue by an incision from one fistulous opening to the other. *2*, Condition present after division of tissue.

3, *2*). The mucous membrane around the rectal fistula was incised and dissected down to the rectum and closed with silver wire sutures. The skin was closed over the inverted edge (fig. 4). A rectal tube was left in the artificial anus, and the patient was returned to her bed in excellent condition.

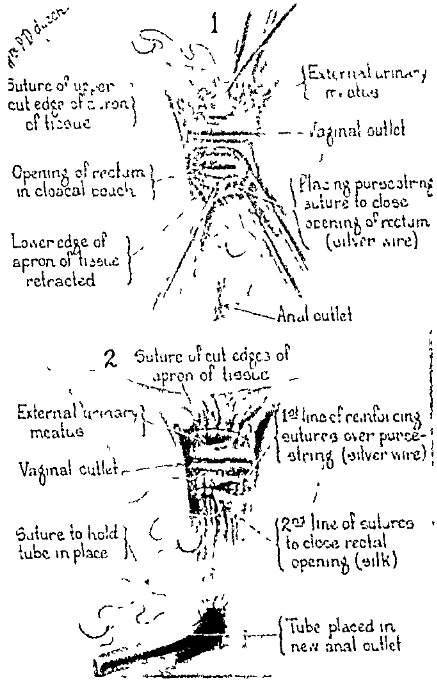
1
Suture of upper cut edge of apron of tissue
External urinary meatus
Vaginal outlet
Opening of rectum in cloacal pouch
Placing pursestring suture to close opening of rectum (silver wire)
Lower edge of apron of tissue retracted
Anal outlet
2
Suture of cut edges of apron of tissue
External urinary meatus
1st line of reinforcing sutures over purse-string (silver wire)
Vaginal outlet
Suture to hold tube in place
2nd line of sutures to close rectal opening (silk)
Tube placed in new anal outlet

Fig 4. Case 1 Closure of fistulas and rectal entrance into cloaca. *1*, Suturing upper cut edge of apron of tissue and placing pursestring suture of silver wire to close anomalous anal orifice. *2*, Cut edges of apron of tissue sutured. Pursestring suture tied, closing abnormal rectal outlet; two lines of reinforcing sutures placed over pursestring. After this operation, patient had a normal urethral opening, vaginal orifice with cervix, and artificial anus with sphincter. *When discharged from hospital, had control of urine and feces*

After this operation, the patient had a normal urethral opening, a vaginal orifice with cervix, and an artificial anus which seemed to have a very good sphincter. It was found that she was unable to tell when her bladder was distended, but she was taught to empty it at regular intervals by pressure over the symphysis and thus was continent and no longer wet the bed. The wound healed well and the artificial anus was dilated daily until she was able to be up and about, with urinary and fecal control. She was discharged on September 3 (3½ months after admission) and returned to her home in a distant town, after her mother had been taught to keep the rectum dilated by the use of a large rectal tube.

On January 15, 1941 (2 years and 4 months later) the patient was readmitted to the hospital for a checkup of her kidney function. She had been followed in the interim and had been advised to have the artificially created rectal sphincter dilated with rubber dilators, which she and her mother had done. During this period she had been extremely well and had learned to void her urine without pressure on the bladder. She had control of her bowels, and the artificial anus and rectum were irrigated daily.

When a flat film was taken, preparatory to intravenous pyelography, many large foreign bodies, which were thought to be rectal tubes, were seen in the bowel. She was accordingly transferred to the Surgical Service where an attempt was made to pass a child's proctoscope so the tubing could be removed. This proving impossible due to the small size of the rectal opening, a laparotomy was done and 7 rectal dilators of various sizes were removed. Convalescence was uneventful and she returned to her home.

Contact was kept with the patient for several years, during which she remained well, had good urinary and fecal control, attended school regularly, and took part in the usual activities of a girl of her age. Then, through some misunderstanding, the patient's rectum was not dilated for a period of a year, and there developed a fistula into the vagina, at the site of the original one.

On July 6, 1945 (approximately 7 years after the original operation), under general anesthesia, the rectum was dilated and the fistula was closed with ribbon gut and chromic catgut sutures. The patient was taught to dilate her own rectum, which she is doing daily, and has a perfectly wonderful result, with a continent rectum and a continent bladder.

Case 2. M.D., a 7 year old white female, was admitted to the Brady Foundation of the New York Hospital on March 23, 1945 for the relief of urinary incontinence.

Since birth it had been noted that she passed both urine and feces through a common opening; that is, there appeared to be no rectum. She frequently doubled up with pain, dribbled urine constantly, but seemed to have control of her feces. There was no history of any illness whatsoever, not even the common cold.

Physical examination on admission was negative save for the perineum and genitalia. There was no evidence of an anal orifice. The vaginal opening was unusually wide and urine trickled from it in a slow, steady dribble.

Excretory urograms on the day after admission showed marked distortion of the right kidney and ureter. The pelvis was greatly enlarged, as were the calyces, which pointed centrally, and the ureter was dilated throughout but particularly at its lower end. The left kidney was not shown in any picture. No contrast fluid showed in the bladder. The impression was of a marked hydronephrosis of a single kidney with dilatation of the ureter and incontinence. X-ray of the pelvis showed spina bifida. See figure 11.

The following day the patient was examined under drop ether anesthesia. The urethra was found to be normally situated but very relaxed. The vagina was the usual depth. The rectal opening was in the vestibule, just below the vaginal orifice (fig. 6, *1*, *2*, *3*). A cystoscope was passed into the bladder without difficulty, but attempts to find the opening of either ureter failed, nor was a ureteral orifice discovered in the vestibule, urethra, or rectum, which were cystoscoped. Indigo carmine, 2.5 cc, injected intravenously, appeared in 5 minutes through the vagina. The cystoscope was removed and the vaginoscope introduced. The appearance of bladder tissue was observed on the roof of the vagina, and an orifice was seen but could not be catheterized.

On April 4 (12 days after admission) the patient was taken to the operating room and the aberrant ureter from her solitary (right) kidney was transplanted into the bladder as follows: A Pfannenstiel incision was made in the left side of the abdomen and carried down through the transverse abdominal muscle and the oblique. The peritoneum was retracted and dissected toward the midline by blunt dissection and the ureter exposed (Fig. 6, *4*, *5*). It was very thick and enlarged. It was dissected down as near as possible to its union with the vagina. By passing a sound through the urethra to the bladder, it was possible to locate the latter, which was very small in size. The bladder was opened, and through a second incision in the posterior wall the ureter was transplanted to this location, using 4 sutures of 000 chromic catgut. A 14 F. catheter was attached to the interior of the bladder and fixed in position. The other end was passed from the bladder through the urethra in order to give the patient good urinary drainage. The bladder was closed by a continuous suture of 0 chromic catgut; 4 gm. sulfadiazine were placed in the wound; and 3 Penrose

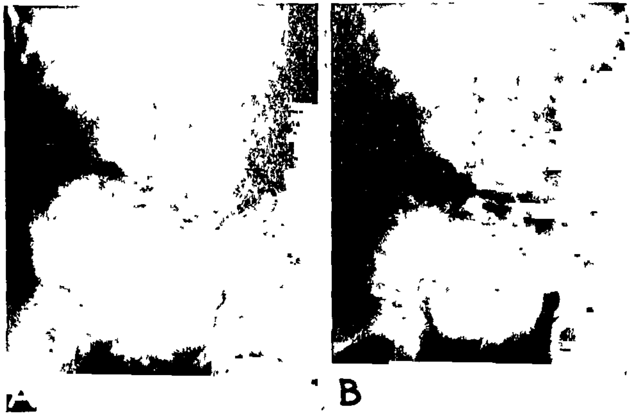

Fig 5 Case 1 Female, 9 years old *A*, Left injection of cloaca before operation; shows shadow-casting material in vestibule of vagina and in bowel *B*, Right cystogram showing normal size bladder

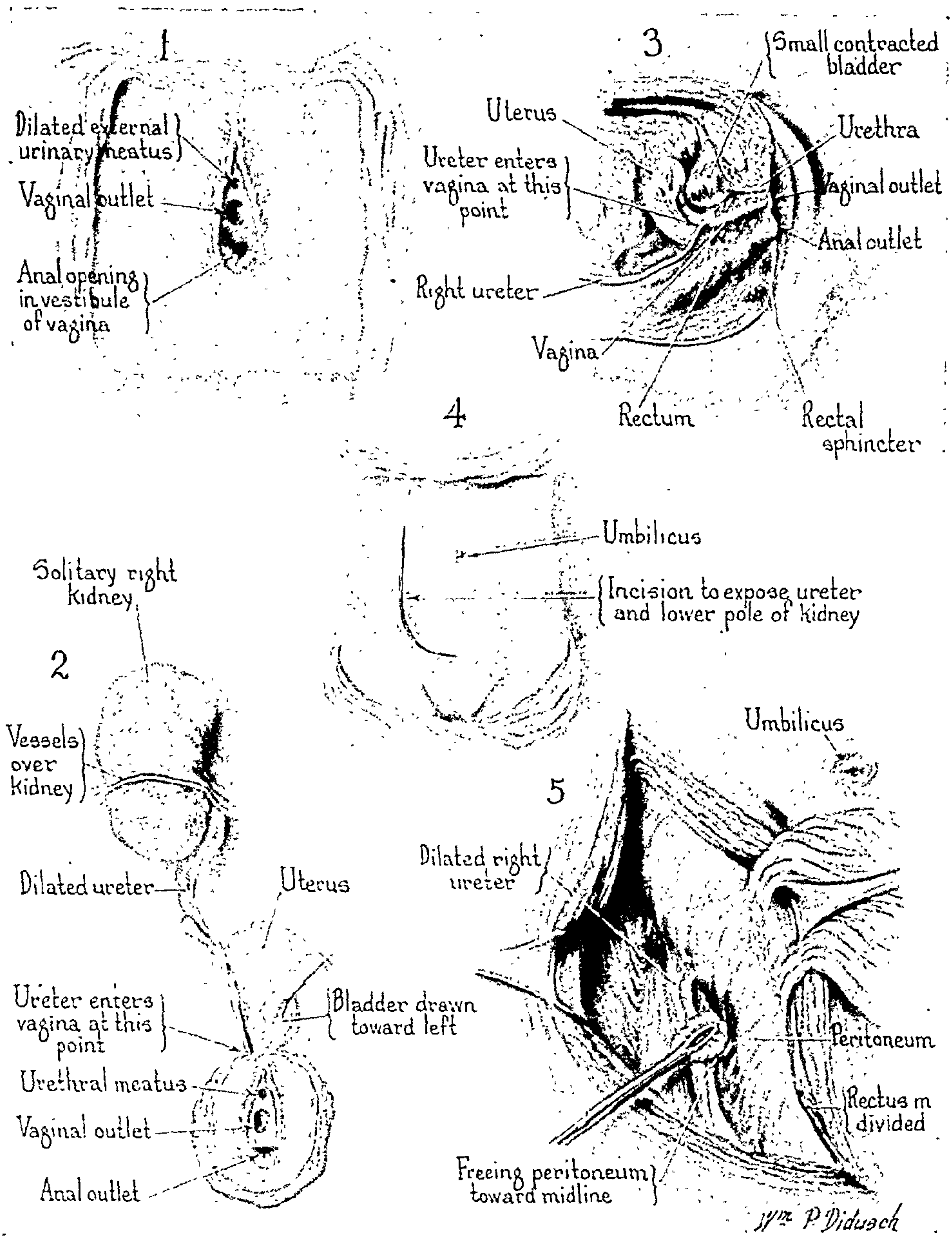

FIG. 6. Case 2. Congenital anomaly, 7 year old female: Single kidney (right) with ureter opening into vagina; rectal outlet in vestibule of vagina. Patient had fecal control but urinary incontinence. *1*, View of dilated urethral meatus, vaginal outlet, and anal opening in vestibule. *2*, Reconstruction of condition found at operation. Solitary (right) kidney with dilated ureter opening into vagina. *3*, Sagittal view showing insertion of ureter into vagina and position of rectal outlet in vestibule. Rectal sphincter muscles present in normal position. *4*, Skin incision to expose ureter and lower pole of kidney. *5*, Exposing dilated ureter.

drains were inserted: one in the lower, one in the middle, and one in the upper portion of the wound. The abdominal wound was closed in layers, and the patient was returned to her bed in good condition (figs. 7 and 8).

Convalescence from this operation was uneventful. The most important aspect of the postoperative nursing care was training the child in urinary control.

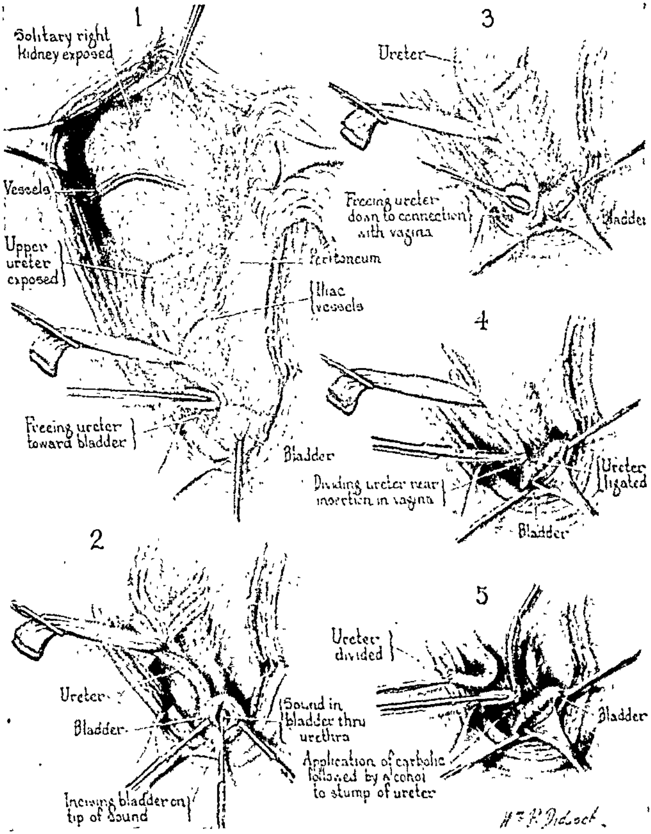
1
Solitary right kidney exposed
Vessels
Upper ureter exposed
Peritoneum
Iliac vessels
Freeing ureter toward bladder
Bladder
3
Ureter
Freeing ureter down to connection with vagina
Bladder
4
Dividing ureter near insertion in vagina
Ureter ligated
Bladder
2
Ureter
Bladder
Sound in bladder thru urethra
Incising bladder on tip of sound
5
Ureter divided
Bladder
Application of carbolic followed by alcohol to stump of ureter

FIG. 7. Case 2. Transplantation of aberrant ureter into bladder. *1*, Kidney exposed; note two vessels over lower pole. Freeing dilated ureter toward bladder. *2*, Incising bladder, which was very small, on tip of sound. *3*, Freeing ureter down to its connection with vagina. *4*, Dividing ureter near its vaginal insertion. *5*, Applying carbolic followed by alcohol to ureteral stump.

She had to be taught to recognize the symptoms of bladder fulness. Because of her very small bladder capacity, she was put on the bedpan every hour during the day and every 2 hours at night. In 2 weeks she had excellent urinary control during the day and was voiding increasing amounts and at 3 to 4 hour intervals.

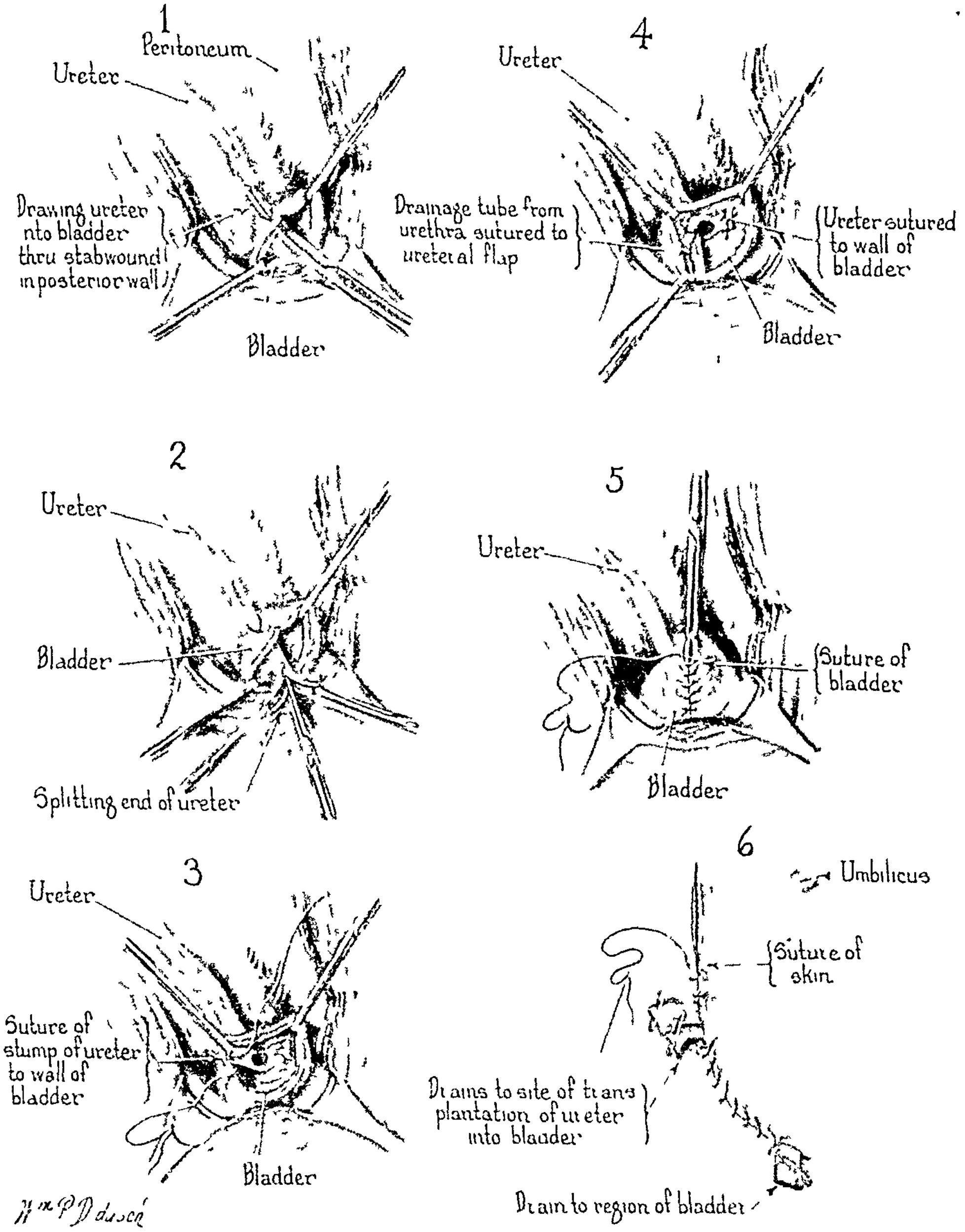
1
Peritoneum
Ureter
Drawing ureter into bladder thru stabwound in posterior wall
Bladder
4
Ureter
Drainage tube from urethra sutured to ureteral flap
Ureter sutured to wall of bladder
Bladder
2
Ureter
Bladder
Splitting end of ureter
5
Ureter
Suture of bladder
Bladder
3
Ureter
Suture of stump of ureter to wall of bladder
Bladder
6
Umbilicus
Suture of skin
Drains to site of transplantation of ureter into bladder
Drain to region of bladder

FIG 8 Case 2 Transplantation of aberrant ureter *1*, Drawing end of ureter through stab wound in bladder *2*, Splitting end of ureter preparatory to suture to bladder wall. *3*, Suturing ureter to bladder wall *4*, Catheter inserted into bladder, tip of catheter sutured to flap of transplanted ureter *5*, Bladder closure. *6*, Wound closure, showing position of drains

On April 25 (3 weeks after the first operation) a plastic operation was done to transplant the rectum from the vaginal vestibule into the perineum. The patient was placed in the lithotomy position, the bowel having been thoroughly prepared in advance. An incision 3 cm long was made in the perineum just above the end of the coccyx. With a Kelly clamp the tissues were separated

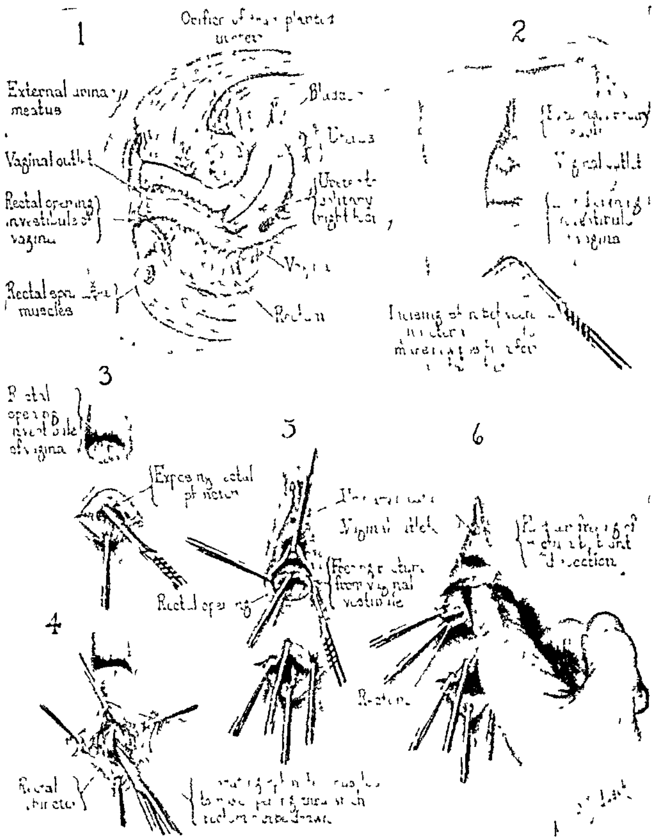
1
Orifice of transplanted ureter
External urinary meatus
Bladder
Uterus
Vaginal outlet
Rectal opening in vestibule of vagina
Vagina
Rectal sphincter muscles
Rectum
2
Vaginal outlet
Rectal opening in vestibule of vagina
3
Rectal opening in vestibule of vagina
Exposing rectal sphincter
4
Rectal sphincter
5
Vaginal outlet
Freeing rectum from vaginal vestibule
Rectal opening
6
Rectum

Fig. 9 Case 2 Second operation. transplantation of rectum from vaginal vestibule into perineum Sphincter
outlet in vestibule of vagina
sphincter 4, Separating sp[illegible]
position in vestibule

down to the muscle of the perineum, the fibers of which were separated carefully by the clamp. An incision was then made around the rectal opening into the vaginal vestibule, carefully extended down, and the rectum separated from the vaginal vestibule for a distance of about 10 cm. (fig. 9). A clamp was inserted through the area in which the rectum was lying freely. The anus was grasped

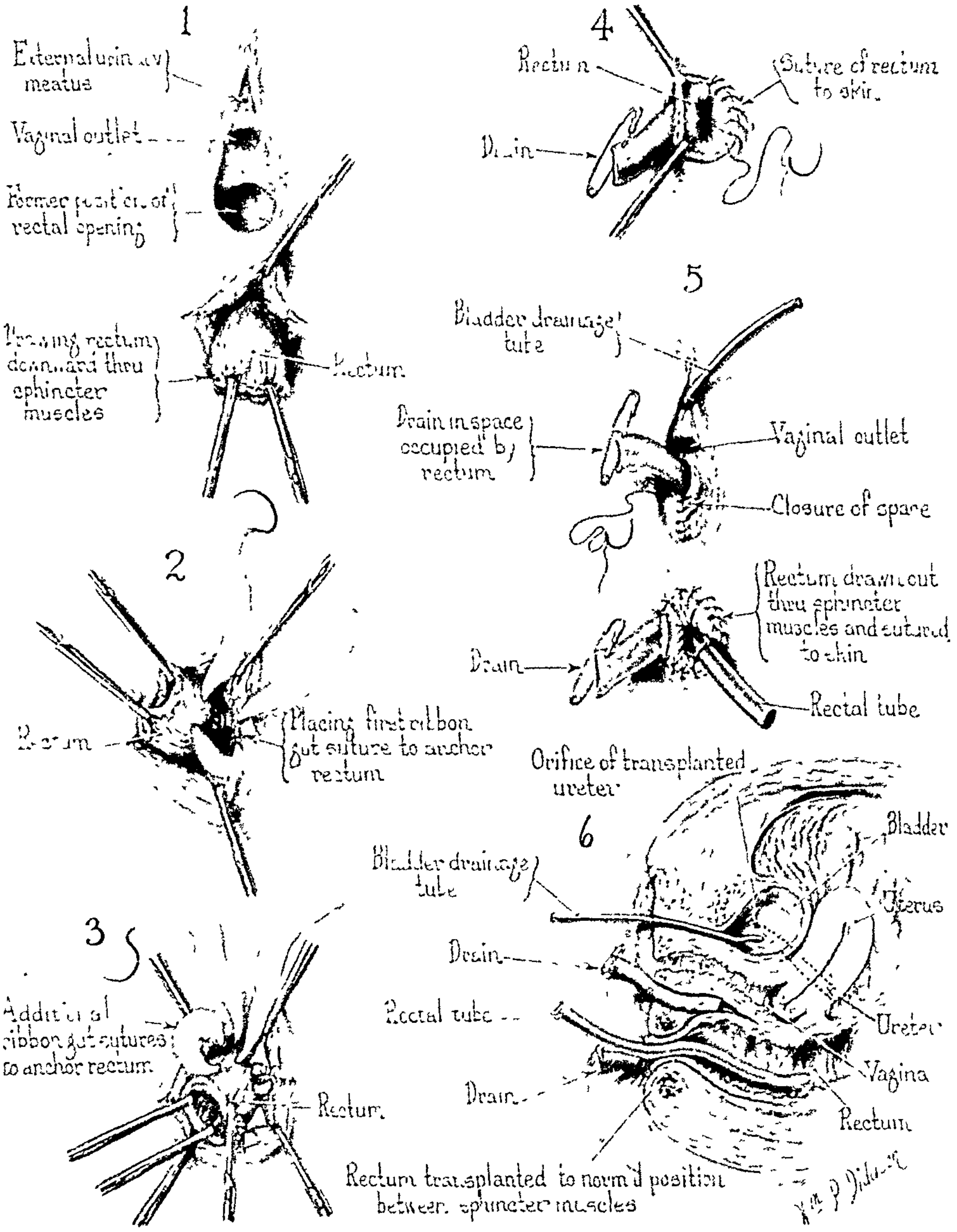
1
External urinary meatus
Vaginal outlet
Former position of rectal opening
Drawing rectum downward thru sphincter muscles
Rectum
2
Rectum
Placing first ribbon gut suture to anchor rectum
3
Additional ribbon gut sutures to anchor rectum
Rectum
4
Rectum
Suture of rectum to skin
Drain
5
Bladder drainage tube
Drain in space occupied by rectum
Vaginal outlet
Closure of space
Rectum drawn out thru sphincter muscles and sutured to skin
Drain
Rectal tube
Orifice of transplanted ureter
6
Bladder
Bladder drainage tube
Uterus
Drain
Rectal tube
Ureter
Vagina
Drain
Rectum
Rectum transplanted to normal position between sphincter muscles

FIG. 10. Case 2. Second operation. *1*, Drawing rectum downward through sphincter muscles. *2*, *3*, Placing 4 ribbon-gut sutures in rectal wall and perineal musculature to anchor rectum. *4*, Suture of anus to skin. *5*, Operation completed, drains in place. *6*, Sagittal section showing condition at close of operation: rectum and anus in normal position in perineum.

by the end of the forceps and drawn through the incision in the perineum. Four ribbon-gut sutures were fixed to the wall of the rectum and to the musculature of the perineum and tied, anchoring the rectum in position. The cut edges

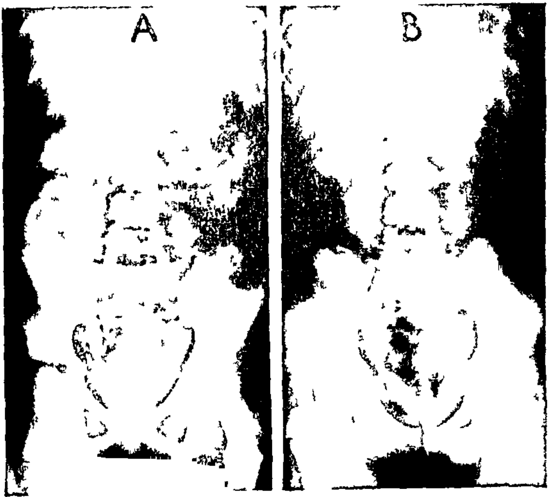

Fig 11 Case 2 Female, 7 years old *A*, Retrograde pyelogram (preoperative) showing distortion and enlargement of solitary (right) ureter which opened into the vagina, also the *hydronephrosis* resulting from the stricture at its lower end *B*, Intravenous pyelogram, 30 *minute* film, 3 weeks after transplantation of ureter to bladder

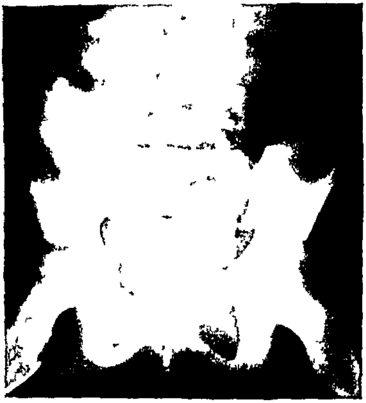

Fig 12 Case 2 Postoperative cystogram Note satisfactory size of bladder, which *never contained urine until after the operation*

of the anus were sutured to the cut edges of the skin by a running suture of chromic catgut Then the incision in the vaginal vestibule was closed with a

Penrose drain extending down about the rectum (fig. 10). The patient was returned to her room in good condition. A 20 F. catheter was fixed in position in the rectum and left there until she had her first bowel movement.

Postoperatively the child was given meticulous perineal care until the wound was entirely healed. She was not allowed to have a bowel movement for 5 days, paregoric being administered in suitable doses. On the evening of the fifth day 1 ounce of castor oil was given her and she had a satisfactory movement, with continence, through the new anus. She continued to have regular bowel movements and her urinary control was excellent. See figure 12. There were no enemas, rectal tubes, or rectal manipulations until her first rectal dilatation, which was done under gas anesthesia 3 weeks after the operation. The only postoperative complication was a blood dyscrasia which necessitated the transfusion of 250 cc blood every few days. This condition, however, was thought to be due to the prolonged administration of sulfadiazine. This drug was withdrawn and the child placed under proper treatment, and eventually her red blood cells increased up to 4 million and she improved greatly, both generally and locally. She was discharged on August 24, 1945, just 5 months after her admission.

The results in this case have been splendid. The patient now has complete continence of urine and feces, and her bladder has become distended so that she holds the normal amount for a child of her age.

SUMMARY

A most important finding in these 2 cases is that, even though a sphincteric muscle cannot be definitely identified, a continent anus may be made by carefully separating the muscle fibers of the perineal floor and fixing the anal wall to the skin of the perineum.

The physical condition of these 2 patients showed rapid and great improvement. They gained weight and strength. The "hang-dog" expression left them and they assumed the appearance and behavior of normal girls of the same age.

The psychological changes were equally notable. Fear and depression gave place to enthusiasm and elation. From miserable and dejected specimens of humanity these children quickly changed to normal, happy girls. At her last checkup, the older girl, and the first to be operated upon, was only a year behind other children of her age in school and was taking an active part in school and church affairs. The younger child during her hospital sojourn responded very well to instruction given her by the excellent teacher sent by the New York City Department of Education (as in the case of all hospitalized children) and since her discharge has been attending school regularly.

CONCLUSION

Persistent cloaca is a rare condition. Two cases in females, treated by operation, are described here, and a search of the literature discloses reports of only four others.

Children thus afflicted are completely ostracized by their condition, and the psychological reaction is so intense that other similar cases should be corrected by surgery at an early age—certainly before the child reaches school age.

The creation of a continent anus was accomplished in both of these cases, and presented no outstanding difficulties.

NOTE

After these two patients had been operated upon, a search of the literature for other cases of human cloaca treated surgically revealed a report of 3 cases (Stone, 1936) which were somewhat similar to these, the differences being that in the first case there was a small rectal opening in the posterior vaginal wall 1½ inches above the hymen, in the second case the rectum opened into the posterior vaginal wall 1 inch above the hymen, and in the third case the rectum opened through the posterior vaginal wall low down.

In 1937 H. H. Young reported a case of a 17 year old male with an imperforate anus, the bowel connecting with the deep urethra, or urogenital sinus, which opened in the perineum behind an hypospadic penis. For 18 months liquid feces escaped through the urinary meatus; then, for 15 years, feces were evacuated through a colostomy. The anus was found to be in normal position beneath the skin and functionally active. A plastic operation was done, separating the rectum from the urethra, excising the skin overlying the sphincter, dilating the sphincter, and then bringing the rectum through it to form a normal anus. Subsequent operations were done to cure the hypospadias and remove the colostomy.

In 1938 Mayo and Butsch reported a case in a female in which the rectum opened into the vagina at the posterior fourchet.

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PROSTATECTOMY IN MEN OVER SEVENTY-FIVE[1]

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It wasn't many years ago that prostatectomy in the older age group was attended with high mortality and morbidity rates. Hugh Cabot wrote in 1936: "Great age is a very serious complication. Whereas the mortality between 60 and 70 is about the same as between 50 and 60, after 75 the mortality of all procedures increases rapidly, and between 80 and 90 is 5 to 6 times as great as between 60 and 70 years." In 1926 Hugh Young and D. M. Davis, writing in *Young's Practice of Urology*, presented 1049 cases of perineal prostatectomy. Thirty-one patients were 80 years or older, or 3 per cent. While the mortality rate for the whole series was 3.4 per cent, in this group the mortality rate was 16 per cent. F. B. Twinem, in his paper on "The Very Aged Prostatic," operated upon 33 patients over 80 between 1921 and 1936, with a mortality rate of 33.3 per cent. In 1935 H. L. Kretschmer wrote: "It is a well known fact and has been repeatedly proven by published statistics of large groups of cases that the mortality in prostatectomies increases with each decade. This fact has deprived some of the patients in the upper group (80 to 95) from being relieved of their obstruction by open operation." At that time he presented a report of 551 resections on 495 cases, 25 of which were over 80, or approximately 5 per cent. Swan and Mintz, in a review of the prostatectomies for benign prostatic hypertrophy at the Massachusetts General Hospital in the years 1926 to 1930 inclusive, had only 1 patient in the series who was 80 or more years of age.

The Veterans Administration Hospital at Bay Pines is located just outside of St. Petersburg, Florida. This section of Florida has through the years become a haven for elderly people. A greater percentage of our patients are in the older age group than is found in the Veterans Hospitals in other sections of the country. There is, in addition, a domiciliary home of 880 beds for elderly and disabled veterans associated with the hospital. The urological service is of necessity larger and the aged prostatic is more often encountered, despite the fact that there are few Spanish American War veterans as compared to World War I and II veterans. In the past 3 years 132 patients had prostatectomies performed on them. The ages ranged from 28 to 90. Nineteen patients, or 14.4 per cent were 75 or over, and 4 per cent were above 80 years of age. No patient was denied prostatic surgery because of age; rather, the patient's general physical condition and cardiac status were used as a yardstick. The majority of patients had x-rays of the chest and electrocardiograms preoperatively. All of them were seen by a cardiologist prior to surgery. Hypertension in itself did not contraindicate surgery. Using the standard classification of heart diseases, patients who fell into classes 1 to 3 who needed surgery were operated on, while class 4 cases were seldom operated on, and class 5 never. While many of our cases had evidence of general or cerebral arteriosclerosis, had hypertension, or gave a history of previous hypertension, there was no significant heart disease in 80 patients. Forty-one patients were classified as having class 1 or 2 hearts, 10 patients fell in the class 3 group, and only one in the class 4.

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In recent years many more men in the age groups of 75 and above are accepting prostatic surgery. Moreover, the mortality rates for this group has decreased. The reasons for this change is the purpose of this paper.

One of the greatest factors in bringing about this change is the advent of the transurethral resection. In the early 1930's this operation became popularized. It was soon learned that what was first regarded as a minor operation was a highly technical procedure which was not easy to master. Many urologists did master the technique with remarkable results. A graphic example is reported by Mercier when he presented the end results of 900 cases of transurethral resection of the prostate. His mortality rates were as follows:

Case	*Percentage*
1-25	32
26-150	7
150-300	5.3
300-500	2.5
500-900	0.7

Lachen and Emmett reported that at the Mayo Clinic between 1934 and 1942 three hundred and forty five patients 80 years or more were treated by transurethral resection. The mortality rate for this group was 2.6 per cent, compared with 1.2 per cent mortality rate for nearly 8,000 resections over the same period of time. This they regarded as showing that patients of advanced age tolerate transurethral resection almost as well as younger men.

The incidence of carcinoma of the prostate increases with advancing age. In the vast majority of cases by the time a diagnosis of carcinoma of the prostate is made clinically, a cure is no longer possible by radical perineal prostatectomy. You all know the difficulties encountered and the poor results that are obtained in some cases when carcinoma of the prostate is treated by suprapubic enucleation or perineal prostatectomy. Many patients who previously would have been denied surgery because of carcinoma are having resections with relief of obstructive symptoms. Many of these patients are over 75. Thompson and Habin, in a review of 1200 cases of patients who were more than 70 years old treated by transurethral resection, showed that 16.4 per cent of that series were proven to have carcinoma of the prostate gland. In the cases treated by resection at Bay Pines, 10.2 per cent proved to have carcinoma. Their paper was published in 1939. Since then, the addition of estrogenic hormones and castration to our armamentarium in the treatment of carcinoma of the prostate has reduced to some extent the need of resections to overcome vesical neck obstruction in some of these cases.

With the popularization of transurethral resection, many controversies arose as to which method of prostatectomy produced the lowest mortality and morbidity rates. Statistics and techniques were being constantly reviewed. This rivalry between advocates of suprapubic, perineal, and transurethral resections caused a more critical analysis of the whole problem with consequent improvement in individual techniques. What was once considered a standard suprapubic prostatectomy has now changed so that each individual urologist has his own technique. The indications for one or two stages vary with the individual. The use of Pilcher bags, various types of Foley catheters, suction, various modifications of Freyer tubes, sump drainage, etc. have all aided in reducing mortality and discomfort. Those men who used trocar cystostomy instead of suprapubic cystostomy prior to prostatectomy, believe their technique has many advantages. Young's classical perineal prostatectomy has been modified by several men who believe their methods give superior results. All this rivalry has been healthy. Volumes have been written about mortality and morbidity rates and comparison of these methods. An example is furnished by a paper on prostatic hypertrophy written by Alcock in 1935, in which he gives a summary of 600 resections and prostatectomies. His general mortality at that time for resections was 4.6 per cent as compared to 22.3 per cent for prostatectomies. Forty-five patients over 80 years of age had resections with a 9 per cent mortality, while 20 patients over 80 years of age had prostatectomies with 35 per cent mortality. Eleven years later, in 1946, Higbee presented 100 cases of each type of prostatectomy with a mortality rate of 5 per cent for suprapubic, 4 per cent for transurethral, and 3 per cent for perineal. In this series, 28 patients were over 80 years of age. Nine had suprapubics with no mortality, 6 had perineal prostatectomy with no mortality, and 13 had transurethral resections with 1 death.

With the discovery of the sulfonamide series, and the newer antibiotics such as penicillin and now streptomycin, the complications and mortality of the various procedures have definitely been diminished so that it is now safer to operate on the older individual. While these drugs will never take the place of adequate drainage and proper surgery in urology, they are nevertheless important in making prostatic surgery less hazardous. In our series they were not used routinely but on a more selective basis.

One of the advantages of transurethral resection is the shorter hospital stay in most cases. To approach this economic factor, methods have been devised to shorten the hospitalization of the patient especially via the suprapubic route. Some statistics would seem to indicate lower mortality rates for 1-stage suprapubic prostatectomies, although it is admitted that generally the poorer risks are done in 2-stages. Stegman had 3 deaths in 60 cases done in 1-stage, while he also had 3 deaths in 10 cases where either trocar cystostomy or regular cystostomy was performed prior to suprapubic prostatectomy. Mortality rates are also as a rule higher in charity or service cases than in private patients. Rolnick and Riskind reported a 24 per cent mortality rate for 2-stage suprapubics, 14.5 per cent for resections, and 11 per cent for perineal prostatectomies in a charity hospital. At another hospital, where both private and ward cases are handled, McCrea reported a 5 per cent mortality in private cases as compared to 17.8 per cent ward deaths. At Veterans Hospitals, many patients apply for admission later than in private practice. The length of hospital stay is secondary to mortality and morbidity rates. In the past 3 years, 36 2-stage suprapubic prostatectomies were performed with 1 postoperative death in a man 80 years old; 6 of these cases were over 75 years of age. In younger men, 5

1 stage suprapubic prostatectomies were performed with 1 death Two patients had suprapubic cystostomies in anticipation for a prostatectomy, and died of pulmonary infarction and coronary occlusion respectively before the second stage could be performed The coronary occlusion occurred in a patient aged 78 If these 2 cases are added to the general mortality rate for suprapubic prostatectomy at our hospital, the mortality rate rises to 9 per cent The mortality rate for all resections has been 2 per cent There was no mortality in the men over 75 who were treated by means of transurethral resection

SUMMARY

Prostatic surgery in the aged has become less hazardous and can be performed with a relatively low mortality rate

Factors involved in changing our concept of prostatic surgery in the aged include a) The lowering of mortality rates through increased experience with transurethral resection techniques, b) the adaptability of transurethral resection to treatment of carcinoma of the prostate has increased the number of aged individuals now accepting surgery, c) critical analysis by advocates of other forms of prostatic surgery has improved techniques to rival the results of resectionists, d) discovery and use of the newer antibiotics, e) recognition of the value of a cardiac consultation preoperatively

In a series of 132 cases of prostatic obstruction treated by surgery, 19 patients were over 75 years of age The general mortality rate for transurethral resections was 2 per cent, and for suprapubic prostatectomy, including 2 cases who did not reach the second stage, was 9 per cent Six aged patients were treated by 2 stage suprapubic prostatectomy with 1 death One patient, 78 years of age, died of coronary occlusion before the second stage could be performed Fourteen resections were done on 12 patients over 75 with no mortality

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had satisfactory results. There were 6 (20 per cent) failures and 3 (10 per cent) deaths. Unfortunately surgeons and gynecologists frequently have not familiarized themselves with the principles of ureteral repair and when confronted with a severed ureter are prone to disregard conservation of the kidney as it is easier to ligate the severed ureter with or without subsequent nephrectomy. A serious objection to uretero-ureteral anastomosis is the probability of the formation of subsequent cicatricial contracture. Many of these patients require frequent and systematic dilatation of the ureter; otherwise slow hydronephrotic atrophy resulting from the ureteral stenosis will in the end necessitate nephrectomy. Good immediate results have undoubtedly been reported from this procedure when the ultimate result was unsatisfactory as illustrated by a case reported by Nora, in which a ureter was accidently severed during hysterectomy and was repaired by an immediate uretero-ureteral anastomosis. Patency of the ureter was maintained by catheter dilatations over a period of eighteen months and on several occasions the case was presented before medical societies as evidence of a good result from ureterorrhaphy. Seven years later Nora performed a right nephrectomy; the ureter had become abruptly stenosed and there was complete destruction of the renal parenchyma.

If the ureter has been severed low in the pelvis probably a better procedure than an attempt at anastomosis of its ends would be its re-implantation into the bladder as low in the base as possible, employing a technic designed to prevent reflux of urine from the bladder. Of 70 collected cases so treated, Adams reported perfect results in 8 (11.4 per cent), fair results (moderate stenosis) in 38 (54.3 per cent), failures in 21 (30.4 per cent) and 3 deaths (4.3 per cent). If the precaution is taken however of dividing the proximal end of the severed ureter 6 or 8 mm. and inserting it at least 1 cm. beyond its entrance into the bladder, subsequent stenosis of the ureteral opening will be less likely to occur.

Cutaneous ureterostomy is mentioned only for condemnation although it may be regarded as a conservative measure. Some writers prefer uretero-intestinal anastomosis. A serious objection is the lack of preparation of the patient for such a procedure with special reference to emptying and cleansing the bowel and the employment of modern chemotherapy in the form of intestinal antisepsis. Therefore, an unplanned uretero-intestinal anastomosis undoubtedly would incur greater risk than a planned operation of this type.

Ligation under certain circumstances may be the operation of choice; after a difficult and prolonged pelvic operation the patient already may have been on the operating table too long in a state of shock. In this event if palpation of the opposite kidney indicates its healthy state ligation may be considered the best and safest procedure although it is freely admitted that palpation of the opposite kidney can yield only presumptive evidence of its functional condition. While performing a major urological operation recently a surgical confrere called me into an adjoining operating room because of a severed ureter incurred during a difficult hysterectomy. He had taken the precaution to mobilize the ureter in spite of which it had been divided accidentally about 10 cm. above the bladder. The patient had been on the table nearly 2 hours and was in no condition for further extensive surgery. It appeared wise to advise secure ligation of the proximal stump after ascertaining by palpation that the opposite kidney appeared sound. The patient made a nice recovery. Temporary ureteral repair might have been considered, however, had I not been engaged with my own patient.

If a large segment of the ureter has been excised uretero-ureteral anastomosis or re-implantation into the bladder usually is not possible and one of the following procedures should be considered: transuretero-ureteral anastomosis, uretero-intestinal anastomosis, ureterocutaneous anastomosis, ligation and nephrectomy, listed in the order of their choice. Hepler prefers uretero-intestinal implantation in such cases to ligation or nephrectomy, employing the Coffey No. 1 technique.

Frequently the extreme condition of the patient prohibits conservative efforts. There should be some temporary measure, less radical than ligation, nephrectomy or cutaneous ureterostomy, which would permit a well-planned conservative operation later when conditions are more favorable. There should be considered for this purpose 1) the passage of a ureteral catheter through the proximal segment of the severed ureter, the distal end of which may be ligated about the catheter employing non-absorbable suture material with extraperitoneal drainage, 2) temporary ureterostomy and 3) temporary nephrostomy. The problem that would then be presented is the same as will be discussed under the second group comprising those injuries discovered in the postoperative period.

MANAGEMENT OF INJURY WHEN RECOGNIZED LATE

Unilateral ligation or ureteral occlusion from acute angulation secondary to sutures probably occurs more often than is generally believed. It may be suspected, however, in the postoperative period following pelvic surgery if there is unusual discomfort in either renal area associated with tenderness at the costovertebral angle. A wider employment of excretory urography in such cases undoubtedly would lead to the more frequent detection of such injuries and would render possible the conservation of the involved kidney rather than to permit atrophy of the organ. In many cases the appearance of urinary leakage from the vagina or from the abdominal incision in the early postoperative period is the first evidence of ureteral injury, either unilateral or bilateral. If both ureters have been ligated or otherwise occluded, complete anuria is at once evident and may be erroneously diagnosed as "suppression of urine." Failure to demonstrate urine in the bladder on catheterization 6 to 12 hours following a difficult pelvic operation renders a cystoscopic examination mandatory for the exclusion of obstructed ureters. Too often the patient will be subjected to treatment for suppression of urine for several days and only with the increasing gravity of the case will a urological consultation be requested in an atmosphere of desperation. If cystoscopy confirms the suspicion of bilateral ureteral occlusion an immediate unilateral nephrostomy may prove to be a life saving measure. Lynch and Thompson prefer temporary ureterostomy to bilateral nephrostomy in bilateral injuries because it is technically easier and avoids the necessity of changing the position of the patient and redraping, as well as ease in locating the distended obstructed ureters and their ready catheterization. With the abdomen open, however, deligation would appear more practical. Regarding deligation, it is interesting to note from a review of the literature the wide divergence of opinion regarding its advisability. A review of 23 articles dealing with ureteral injury discloses that 8 writers definitely advise against deligation; it is advocated by 11 and 4 do not mention it. Hepler states that "postoperative deligation is a formidable operation with a mortality rate of about 90 per cent." Feiner reports the death of 2 patients following intra-abdominal deligation and is of the opinion that nephrostomy with subsequent operation for ureteral anastomosis or re-implantation into the bladder is a safer procedure. Deligation as it is usually practiced by the average surgeon with the patient in a desperate condition, and without the assistance of a urologist, is undoubtedly hazardous in that the abdomen is re-opened and the surgeon carries out an extensive search for offending ligatures, which may be extremely difficult to locate. Enlisting the co-operation of a urologist when the surgeon re-opens the abdomen is of extreme importance, the value of which cannot be overemphasized. With ureteral catheters, preferably of a large caliber (9 or 11 F.), the cystoscopist can literally prod the obstructed points, permitting the surgeon to quickly clip ligatures and also facilitating the detection of more than one ligated point if present. He should not be satisfied until both catheters have passed into the renal pelves. Such active urological assistance should render deligation a far less hazardous procedure.

ILLUSTRATIVE CASES

Mrs. H. B., aged 40, was first seen February 19, 1945. She had undergone a difficult hysterectomy by a general surgeon 3 days before. There was 200 cc of urine in the bladder on catheterization 15 hours after the operation and complete anuria since, for which she had been treated for "suppression of urine." By the time of the urological consultation she had moderate generalized edema and was semicomatose. The nonprotein nitrogen content of the blood was estimated at 172.5 mg. per cent and the creatinin estimation was 3.5 mg. per cent. Cystoscopy revealed impassable obstructions of both ureters approximately 7 cm. above the bladder. In my absence from the city one of my associates performed an immediate left nephrostomy, which permitted the drainage of 1800 cc of urine during the following 18 hours. Upon my return 3 days following the nephrostomy I advised immediate deligation. The surgeon re-opened the abdomen; I passed a cystoscope and inserted No. 11 ureteral catheters into each ureter and easily located the ligated points for the surgeon, who clipped sutures at these points releasing the obstructions and permitting the catheters to pass with ease to both renal pelves. The catheters were left in place and the abdomen was quickly closed. Her convalescence was uneventful. The catheters and nephrostomy tube were removed after 7 days and she was discharged from the hospital 16 days following the deligation, at which time the nonprotein nitrogen estimation on the blood was 35 mg. per cent. Eighteen days later a 10 F. bulb was passed through each ureter without detecting any evidence of obstruction and there was no abnormal retention of urine in either renal pelvis. Two years later an excretory urogram was obtained, revealing normal bilateral function and outline, including normal ureters (fig. 1).

Comment: It is evident that if nephrostomy drainage had been depended upon *for a longer period that severe ureteral damage from the ligatures would have* been inevitable. Cystoscopic assistance when the abdomen was re-opened largely eliminated the risk of deligation and its early accomplishment undoubtedly was the chief factor in the good result obtained.

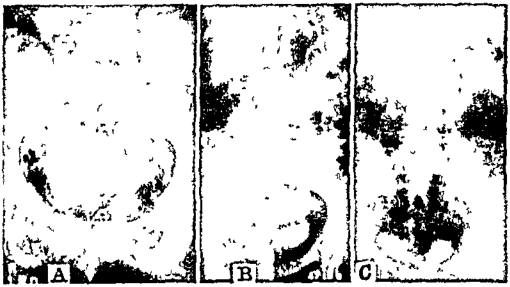

FIG. 1. *A*, Plain film, revealing ureteral catheters and indicating points of complete obstruction in both ureters at level of brim of pelvis. *B*, Retrograde bilateral pyelograms obtained during second postoperative week after deligation. *C*, Excretory urogram obtained 2 years later, revealing normal bilateral function and normal ureters.

In those cases in which there is evidence that the ureter has been severed, incised, resected or crushed with subsequent sloughing the development of urinary leakage in the postoperative period may be the first indication of the accident, whether unilateral or bilateral. The problem then resolves itself into conserving the life of the patient as well as conservation of the involved kidney. *Extensive urinary extravasation may occur from a severed ureter which was* neither recognized nor ligated. However, in most cases urinary drainage will appear within a few days, either from the incision or from the vagina, with consequent improvement of the patient's status. Weeks or months may elapse before a urological consultation is requested because of the hope that spontaneous closure of the fistula will occur. In such instances urologists should determine by cystoscopy or excretory urography, or a combination of both, the extent of the damage and the side affected if unilateral. Some surgeons follow the line of least resistance and perform a nephrectomy, which not only controls the annoying urinary leakage but diminishes to some extent the prospect of medicolegal complications. The majority of urologists, however, are keenly aware of the desirability of conserving renal tissue and when their assistance is enlisted their efforts as a rule are along conservative lines. It is usually impractical to attempt an end-to-end anastomosis of a severed ureter when it has been discovered late If the site of the injury is low in the pelvis, the proximal ureter may be mobilized, permitting sufficient elongation to enable its re-implantation into the bladder at a site preferably as low in the base as possible and with the distal 3 or 4 cm. of the ureter buried in its musculature before finally emerging through the mucosa, thus preserving valve-like function which is so essential in protecting the kidney from vesical reflux.

Mrs. P. M. W., aged 46, was first seen on January 23, 1943. She had undergone a hysterectomy for multiple fibromyomata 3 months before. The immediate postoperative period was stormy and after a few days urine began to drain continuously from the vagina, along with profuse purulent drainage from the abdominal incision. Since then urine had not been voided in a normal way. The referring surgeon stated that he was aware that he had accidently severed the left ureter, the proximal stump of which was ligated with catgut. He was unable to account for her inability to void nor the discharge of urine from the vagina. Examination revealed absence of urine in the bladder. There was no secretion from either ureteral orifice, complete obstruction of the left ureter 2 cm. above the bladder and a similar obstruction of the right ureter 4 cm. above the orifice. An excretory urogram proved very informative. The soft tissue shadow of the right kidney appeared essentially normal; several moderately dilated calyces were filled with the medium, but the renal pelvis and ureter could not be visualized. The left ureter was open in spite of its having been ligated and the kidney was of essentially normal function, but the urine was draining through the vagina. In view of these findings it was assumed that the right ureter had been ligated 4 cm. above the bladder and in spite of its complete occlusion for 3 months it was astonishing to find that it appeared functionally worth conserving. It was therefore explored first and was found involved in dense scar tissue in the region of the vault of the vagina where it evidently had been incorporated in sutures. Although it was about 1 cm. in diameter above the ligated point, it was amputated at this site and mobilized a distance of 4 or 5 cm., permitting its re-implantation without undue tension low in the right base of the bladder with preservation of a valve-like mechanism. Extraperitoneal rubber tissue drainage was provided through a stab wound and the incision closed. Her convalescence was satisfactory and 9 days later an extraperitoneal approach was made to the left ureter, which was found to have been severed at a point opposite the second sacral segment. It was freely mobilized for a distance of 5 or 6 cm. and it was possible to also re-implant it into the bladder without undue tension at a site low in the left base, employing essentially the same technique as was carried out on the opposite side. Continuous catheter drainage of the bladder was provided for 10 days. Her convalescence was uneventful and on the seventeenth day, upon filling the bladder with radiopaque fluid, there was no evidence of ureteral reflux on either side. Indigo carmine appeared from the right in 13 minutes and from the left in 14 minutes in fair concentration. She was dismissed 31 days following the first operation. Twenty-seventh months later she returned for a check-up at our request. The urinalysis was negative. There were no urinary complaints and an excretory urogram disclosed both kidneys of normal function and outline (fig. 2).

Comment: It is truly remarkable that the right kidney which had evidently been completely occluded for 3 months should display such recuperative ability when release of the obstruction was accomplished. Fortunate indeed was the spontaneous opening of the ligated left ureter, thus providing urinary drainage from 1 kidney and preservation of life. It is worthy of note that the sites of the injuries to the ureters were sufficiently low, aided by mobilization of essentially their lower thirds, to permit re-implantation into the base of the bladder without undue tension and with a good functional result.

Althought accidental injury of the ureter is usually incurred in those cases where removal of organs or tissues is necessary it is of interest to note that the ureters may be accidentally damaged in cases where tissues have not been removed, for example in such operations as uterine suspension. Simple ligation or acute angulation from sutures would be the most plausible explanation in such cases.

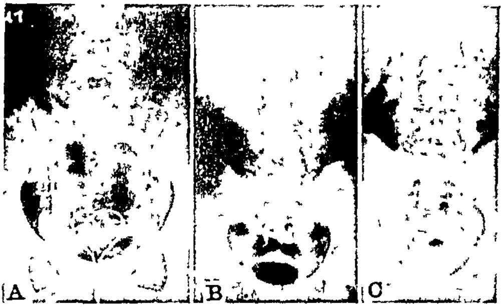

FIG 2 A, Note catheters in place, indicating sites of ureteral obstruction at level of brim of pelvis on right and at a lower level on left side. *B*, Excretory urogram, indicating good function and drainage from left and surprisingly good function from right in spite of obstruction *C*, Excretory urogram obtained 27 months following re-implantation of both ureters into bladder, *indicating normal bilateral function and normal ureters.*

Mrs R. V. K , aged 27, was first examined on October 12, 1945. She had undergone a suspension of the uterus by a general surgeon 2 months before. A few days later an almost constant aching pain developed in the left loin. The pain persisted after her return home and 1 month after she left the hospital cystoscopy elsewhere revealed no evidence of function of the left kidney and its removal was advised by the same surgeon. She was also told that there was a stricture of the right ureter. She decided to obtain another opinion before undergoing a left nephrectomy. My examination revealed a point of marked narrowing in the right lower ureter, with ureterectasis and pyelectasis of moderate degree, 75 cc of clear urine was aspirated from the right renal pelvis. An obstruction was met in the lower left ureter 1 cm. above the bladder; after considerable effort a No. 5 catheter was passed beyond the obstruction and 170 cc of clear urine was aspirated. Pyelography disclosed an extremely narrow point near the midline corresponding to the point of obstruction 4 cm. above the bladder, above which an extreme degree of ureterectasis and pyelectasis was visualized. Apparently the left ureter had been completely ligated at the time of the uterine suspension and the right lower ureter had possibly been transfixed or partially ligated at the same time. In spite of the extreme degree of damage incurred on the left side conservation of this kidney was highly desirable because of the hydronephrotic state of the opposite kidney. The scar of the previous laparotomy was excised and an extraperitoneal approach made to the left lower ureter. It was identified at the level of the brim of the pelvis, was about 2 cm. in diameter and was mobilized and traced to a point of dense cicatricial obstruction about 3.5 cm. below the pelvic brim. It was divided above the obstructed point and the distal stump ligated. More extensive mobilization permitted its reaching a point in the left base of the bladder about 2 cm. posterior to the left ureteral orifice, where it was re-implanted without undue tension and with preservation of a valve-like mechanism. Because of the advanced degree of ureterectasis a temporary ureterostomy seemed wise and was accomplished by inserting a 14 F. rubber catheter to the renal pelvis introduced through a small opening immediately above the point of anastomosis. The ureterostomy tube and rubber tissue drains were brought out through a small stab wound in the left lower quadrant and the median incision was closed. The ureterostomy tube was removed on the tenth day. There was no urinary leakage from this site. Her convalescence was satisfactory and seventeen days following the operation the right ureter was dilated to 12 F. The re-implanted left ureter appeared to have healed satisfactorily. She was dismissed on the nineteenth postoperative day. She returned for observation 3 months later, at which time the urinalysis was negative and on cystoscopic examination there was only 5 cc of retention in the right renal pelvis and 8 cc on the left side. Phenolsulfonphthalein appeared after 3 minutes from both sides with an output of 24 per cent from the right and 14 per cent from the left in 15 minutes. There were no urinary complaints and she considered herself well. Seven months later the urinalysis was still negative. Excretory urograms revealed both kidneys of essentially normal outline and normal function (fig. 3).

Comment: In spite of the extreme degree of damage incurred by the left kidney from occlusion of the lower ureter of 2 months' duration its return to an essentially normal condition was astonishing and again well illustrates the recuperative ability of the kidney, thoroughly justifiying conservative efforts. Except for the finding of a moderate degree of hydronephrosis on the right side a left nephro-ureterectomy might easily have been considered the operation of choice in this case.

When the ureter has been injured at a high level or a segment accidentally resected, or if it has undergone sloughing through extensive injury to the muscularis or through interference with its blood supply, the problem is definitely more complicated. In such cases it appears that the majority of writers mention the following procedures in the order of their desirability: 1) ligation, 2) nephrectomy, 3) cutaneous ureterostomy and 4) uretero-intestinal anastomosis, although Hepler believes these should be in the inverse order with preference given to implantation into the bowel, a procedure which is also advocated by McIver To this list of available procedures I should like to add transuretero-ureteral anastomosis A number of years ago Sharpe demonstrated experimentally on dogs the feasibility of this operation in which 1 ureter is brought across the midline and anastomosed to the opposite one In 1934 Higgins reported a case in which this operation was performed for the first time on the human In his case there was an incompetent right ureterovesical valve permitting reflux of urine accompanied by severe pain The ureter was severed near the bladder and transplanted into the opposite one with a brilliant postoperative result Smith and Smith in 1941 reported the employment of this procedure in 2

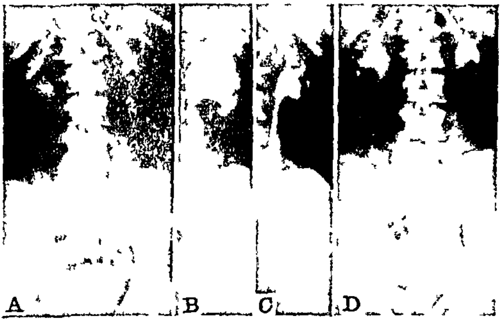

Fig 3 A, Excretory urogram, disclosing point of narrowing of right ureter at brim o
pelvis with moderate degree of ureterectasis and pyelectasis Absence of medium, left
B Left retrograde pyelo
of lower left ureter *C*,
Note ureterostomy tube
tory urogram obtained
dilating right ureteral stricture Note normal bilateral function and essentially normal ureters

additional cases In one an end-to end anastomosis of the ureter had been performed because of an accidentally severed ureter, for which the patient had required frequent ureteral dilatations A long period of recumbency because of a severe fracture enforced discontinuance of the dilatations, after which an impermeable stricture had developed The ureter was severed above the site of stenosis and was anastomosed to the opposite ureter, following closely the technique described by Higgins with the exception that a side-to side anastomosis was made rather than end-to side The same procedure was employed in Smith's second case because of a ureterovaginal fistula resulting from severance of the ureter about 2 inches above the bladder, which occurred during the repair of cervical lacerations Excellent results were obtained in both cases. I have been unable to discover in the literature any other references to transuretero-ureteral anastomosis but I am convinced that it should be of definite value as a means of conserving the kidney when the ureter has been extensively damaged or severed at a level too high to permit ureterovesical re-implantation. There is good reason to list this operation high in the order of desirability of those procedures available for high ureteral injuries and it was so employed in one of my cases.

Miss M. O., aged 33, was first examined by us on January 10, 1946. She had undergone a total hysterectomy 6 weeks before because of multiple large fibromyomata of the uterus. There had been complete anuria for 3 days when urological consultation elsewhere was requested. Their examination revealed the following data: Upon attempting an excretory urogram there was no evidence of medium in either renal area after 30 minutes. Cystoscopy revealed both ureters completely obstructed about 4 cm. above the left orifice and somewhat higher on the right. The resident urologist performed bilateral pyelostomy, after which her condition steadily improved. Six weeks later I was called in on the case when the catheter in the right pyelostomy had been accidentally removed and could not be replaced, for which I advised a right nephrostomy. Eight days later the catheter in the left pyelostomy was also accidentally removed, at which time the decision was made to attempt re-implantation of the left ureter into the bladder. Cystoscopy at this time indicated the obstruction of the left ureter was sufficiently low probably to permit this procedure. An excretory urogram disclosed good bilateral renal function. Eighty days following the hysterectomy I exposed the lower left ureter through an extraperitoneal approach and on tracing the ureter downward it became completely detached, indicating that it had been completely severed and ligated at the original operation. The stenosed end was removed and the wall of the ureter was divided about 1 cm. It was widely mobilized, after which it could be brought to the region of the trigone without excessive tension. It was re-implanted at this site employing a technique somewhat similar to the Coffey No. 1 for uretero-intestinal anastomosis. The left nephrolumbar urinary fistula promptly closed and convalescence was satisfactory. The right nephrostomy was functioning well and she was permitted to return home for further recuperation. Five months later she was re-admitted to the hospital, having gained in weight and strength. She was extremely anxious to be relieved of the right nephrostomy tube. A right nephrectomy was considered but the idea was abandoned because the verdict of time had not been rendered on the ultimate functional result of the re-implanted left ureter. Exploration of the occluded right ureter was decided upon. Although it was obstructed 7 cm. above the bladder, there was a possibility that it might be re-implanted into the bladder or into the colon. In the extreme Trendelenburg position the intestines were packed off and the posterior peritoneum over the region of the ureter divided. It was mobilized downward to the point of obstruction where there was evidence that it had been severed and ligated. In spite of wide mobilization the length was insufficient for re-implantation into the bladder. It was found, however, that it would easily reach the dilated spindle portion of the left mid-ureter and that transuretero-ureteral anastomosis appeared more desirable and less hazardous than uretero-intestinal implantation.

The mid-portion of the left ureter was exposed through a second incision in the posterior peritoneum and with a curved forcep a tunnel beneath the posterior peritoneum was made across the spine, through which the free end of the right ureter was drawn. The end of the right ureter was cut obliquely at about 45 degrees and was anastomosed to an opening in the left ureter about 12 mm. in length, employing interrupted sutures of 0000 chromic catgut. Through a small opening in the right ureter proximal to the anastomosis a No. 5 ureteral catheter was passed through the anastomosis down the lower left ureter into the bladder and the upper end was passed into the right renal pelvis and left in place as a splint The ureterotomy was closed tightly and a small rubber tissue drain was passed extraperitoneally through a small stab wound in the left flank Both posterior peritoneal incisions were closed and the abdominal incision was closed without drainage Following the operation a cystoscope

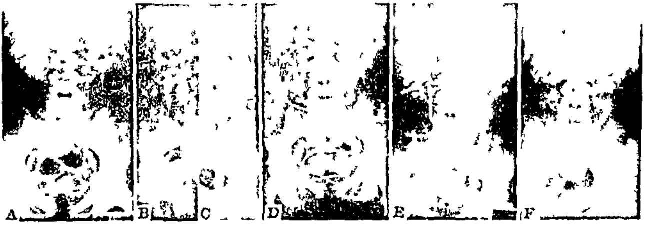

FIG 4 A [illegible] lower left ureter and extravasation in [illegible] e occlusion of right ureter at brim of pel[illegible] [illegible]ntation of left ureter into bladder *D*, [illegible] anastomosis with inlying catheter coiled in bladder prior to its removal passing into lower left ureter and across to right kidney Clamp is on right nephrostomy tube. *E*, Retrograde pyelogram obtained prior to removal of right nephrostomy tube, disclosing right ureter anastomosed to left at level of fifth lumbar vertebra *F*, Excretory *urogram made 5 months following trans-uretero ureteral anastomosis*, indicating good bilateral function and absence of stasis.

was passed and the end of the catheter coiled in the bladder was brought out through the urethra. There was evidence of pyelonephritis for the next 20 days with temperature as high as 103° F. at times. Cystoscopy disclosed that this involved chiefly the left kidney, for which an inlying catheter was inserted, combined with chemotherapy, with prompt improvement. The right nephrostomy tube was removed 11 days later with prompt healing of the site and she was dismissed from the hospital on the forty-fourth postoperative day. A recent postoperative check-up, 5 months following operation, revealed a very satisfactory functional result as evidenced by an excretory urogram indicative of good bilateral renal function and absence of ureterectasis or pyelectasis (fig. 4). The nonprotein nitrogen estimation on the blood was 40 mg. per cent. There were no complaints referable to the urinary tract although a catheterized specimen revealed a moderate degree of pyuria. The re-implanted left ureter easily admitted a 11 F. catheter.

Comment: As far as I have been able to determine, transuretero-ureteral anastomosis has been employed in only 4 cases, including the one herewith reported. The functional result in all of them has been eminently satisfactory and the procedure probably deserves more frequent use as a conservative operation with special reference to injuries of the ureter at levels too high above the bladder to permit re-implantation.

SUMMARY

The principles governing the management of surgical injury of the ureter are determined to a great extent by their early or late discovery and the nature and site of the injury.

In instances of complete anuria following extensive pelvic surgery, the possi bility of bilateral occlusion of the ureters should be considered early rather than the adoption of therapy under the erroneous diagnosis of suppression of urine.

In such cases although deligation as has been employed in the past has been attended by a very high mortality rate, it is believed that the active co-operation of a cystoscopist when the abdomen is re-opened would render the operation far more safe.

Re-implantation of the ureter into the bladder may be considered preferable to uretero-ureteral anastomosis. The latter with its tendency to cicatricial stenosis at the site of anastomosis often sentences the patient to the necessity of numerous subsequent cystoscopic treatments and ureteral dilatations.

When a ureter has been severed or damaged, sacrifice of the involved kidney by ligation or nephrectomy is to be condemned except under most urgent circumstances.

Transuretero-ureteral anastomosis may be considered along with ligation, nephrectomy, cutaneous ureterostomy and uretero-intestinal anastomosis as a measure to be adopted when the ureter has been extensively damaged or severed at a high level. Of these procedures transuretero-ureteral anastomosis would appear the most desirable.

Four cases are cited from the author's experience illustrative of various measures to be adopted in the conservative treatment of the surgically injured ureter. In all of these both ureters were involved. Late follow-up findings are included, indicative of satisfactory functional results in all. There was no mortality.

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BLADDER TONUS IN SPINAL SHOCK[1]

REED M. NESBIT AND JACK LAPIDES

From the Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan

When the spinal cord is injured, there is an immediate loss of sensation and complete flaccidity of the skeletal muscles below the level of trauma; and also urinary retention with subsequent overflow incontinence. These alterations of function are due to the abolition of all motor and sensory impulses, both visceral and somatic, below the lesion and the condition has been termed spinal shock. Spinal shock is said to persist until the paralyzed skeletal muscles exhibit a return of reflex activity.

The urinary retention which occurs during spinal shock has heretofore been ascribed to primary atony of the bladder[2,3,4,5,6], an assumption no doubt prompted by the belief that bladder muscle and skeletal muscle behave in an identical manner. But the two structures are made up of different types of tissue; the bladder is plain muscle and the skeletal muscles are striated. Furthermore they are innervated by different nervous systems. Neuroanatomists believe that the motor impulses to the bladder are mediated entirely over the autonomic nervous system and investigations[7] which we have recently conducted at the University of Michigan Hospital have substantiated this theory. It is well known that plain muscle retains its tonicity and even rhythmic contractility when completely deprived of all of its external innervation. Striated muscle, however, becomes flaccid and elongated when its motor nerves are interrupted. It would be indeed unusual therefore for the bladder, composed of non-striated muscle, to become flaccid when its motor nerve supply has been interrupted, either following spinal cord injury or by chemical blockade; and the observations which we have made both in the clinic and laboratory bear out this view.

The investigations which constitute the basis for the present report demonstrate conclusively that the bladder does not become flaccid when its motor nerves are paralyzed either by chemical interruption or by trauma, but that it retains its normal tonicity under these conditions. To be sure investigators have regularly found distended bladders in paralyzed patients to exhibit decreased tonicity and have doubtless ascribed the flaccidity to spinal shock; but one might reasonably inquire whether the bladders found in this condition are merely decompensated from prolonged distension. We believe that is the case.

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[1] Presented at annual meeting, Southeastern Section, American Urological Association. Palm Beach, Fla., March 27, 1947.

[2] Holmes, G.: Brain, **56**: 383, 1933.

[3] Walker, J. W. T.: Lancet, **1**: 173, 1917.

[4] Fearnsides, E. G.: Brain, **40**: 149, 1917.

[5] Munro, D., and Hahn, J.: New Eng. J. Med., **212**: 229, 1935.

[6] Riches, E. W.: Brit. J. Surg., **31**: 135, 1943.

[7] Nesbit, R. M., Lapides, J., Valk, W. W., Sutler, M., Berry, R. L., Lyons, R. H., Campbell, K. N. and Moe, G. K.: J. Urol., **57**: 242, 1947.

METHODS

Cystometry was utilized in evaluating the status of the bladder tone. The apparatus consisted of a two eyed soft rubber catheter which was connected to a water manometer calibrated in centimeters. Distilled water from a graduated reservoir was allowed to flow into the bladder at an approximately constant rate of 30 cc per minute and pressure volume relationships recorded.

Observations were first made on patients in whom the motor impulses to the bladder had been blocked chemically by the tetra-ethyl ammonium ion. Acheson, Moe and Perera[8, 9, 10] demonstrated that the quaternary ion, tetra ethyl-ammonium, produces a blockade of both sympathetic and parasympathetic ganglia. Investigations[7] conducted during the past year at the University of Michigan Hospital have demonstrated that the tetra ethyl ammonium ion blocks the conduction of motor impulses to the urinary bladder in man. Then cystometrographs were obtained on patients in whom both the sensory and motor supply to the bladder had been abolished by spinal anesthesia. Animal experimentation was also performed in which cystometrographs were obtained on the dog under light nembutal anesthesia, spinal anesthesia, and following transection and crushing of the sacral cord. Finally the bladders of 6 patients in spinal shock were investigated, these patients were all placed on inlying urethral catheter drainage shortly following injury to the spinal cord.

RESULTS

Figure 1, *A* demonstrates the cystometrograph of a normal bladder. The patient had normal sensation to heat, cold, filling and distention. It will be observed that the tonus of the bladder is within normal limits and that the bladder accommodates to increasing volumes of fluid at the same intravesical pressure. After 500 cc of fluid had been allowed to flow into the bladder, the patient indicated an intense desire to micturate, the bladder was then emptied voluntarily and had no residual urine. Intravenous administration of 500 mg of tetra-ethyl-ammonium bromide resulted in an abolition of the voiding contraction of the detrusor but no change in its tonus, accommodation or sensation was observed (fig 1, *B*). No change in bladder tonus was noted in any of the bladders whose motor impulses were blocked at the ganglia by the tetra ethyl-ammonium ion.

Cystometrographs made on the human subject before and during spinal anesthesia are demonstrated in figure 2. It will be seen that the curve prior to spinal anthesthesia exhibits uninhibited contractions and indicates a voiding contraction at 250 cc vesical volume. Spinal anesthesia abolished the uncontrolled contractions of the bladder as well as sensation, but no changes were observed in tonus or accommodation.

Having demonstrated that chemical blockade of the motor impulses in human patients does not result in a decreased tonicity of the detrusor muscle, experi-

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[8] Acheson, G H. and Moe, G K J Pharmacol and Exper Therap , 84: 189, 1945

[9] Acheson, G H and Perera S A J Pharmacol and Exper Therap 87: 273, 1946

[10] Acheson, G H and Moe, G K J Pharmacol and Exper Therap , 87: 220, 1946

ments will now be described in which the dog was the experimental subject. Figure 3, *A* is the cystometrograph obtained on a 13 kilogram dog under nembutal anesthesia. It can be observed that the bladder accommodates normally to increasing volumes of fluid at a water pressure of approximately 12 centimeters. Bladder capacity is 75 cc, at which volume the voiding contraction occurred. A laminectomy was then performed and procaine injected through the dural sheath into the area surrounding the spinal cord. In figure 3, *B* can be seen the reaction of the bladder to increasing volumes of fluid under spinal anesthesia. It will be noted that the curve is exactly the same as that in figure 3, *A* with the exception that the voiding contraction is absent and instead there is a straight line relationship between volume of fluid and intravesical pressure (*A*,*B*). This occurs when the bladder is stretched beyond capacity and merely illustrates the reaction of the elastic connective tissue of the bladder wall to increasing volumes of fluid. Spinal anesthesia has eliminated the segmental reflex at sacral level 2, 3 and 4 and thus no motor impulses can be transmitted to the detrusor muscle to cause it to contract when bladder capacity is reached.

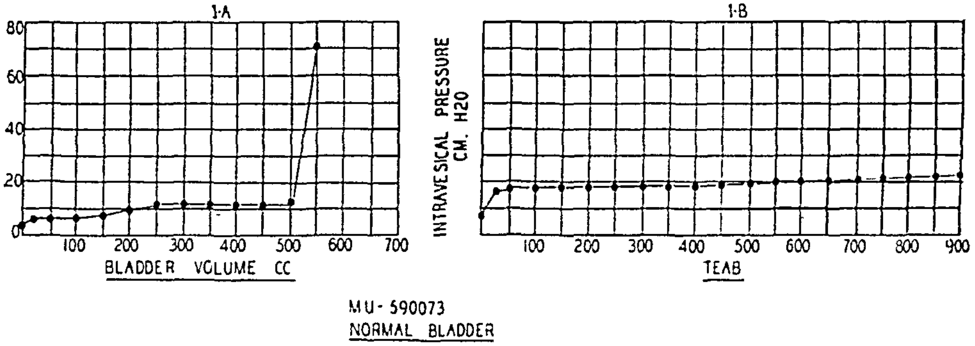


FIG. 1

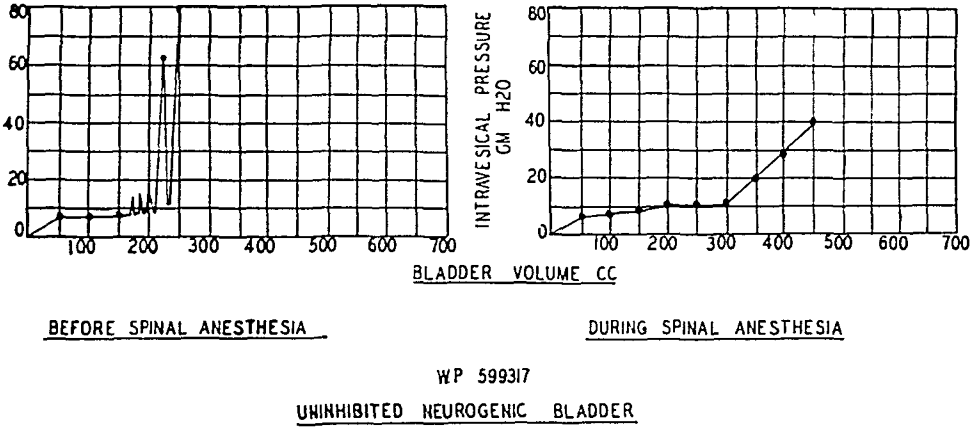


FIG. 2

The dog's spinal cord was then transected at the level of spinal segment L2 and the portion below the transection was thoroughly crushed. Following this procedure all of the skeletal muscles below the level of cord injury became flaccid.

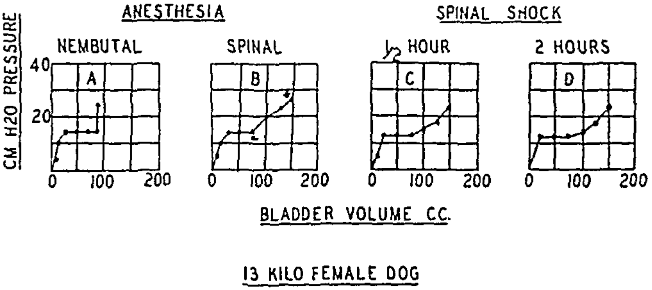

ANESTHESIA
SPINAL SHOCK
NEMBUTAL
SPINAL
½ HOUR
2 HOURS
CM H20 PRESSURE
40
20
A
B
C
D
0
100
200
BLADDER VOLUME CC.
13 KILO FEMALE DOG

Fig. 3

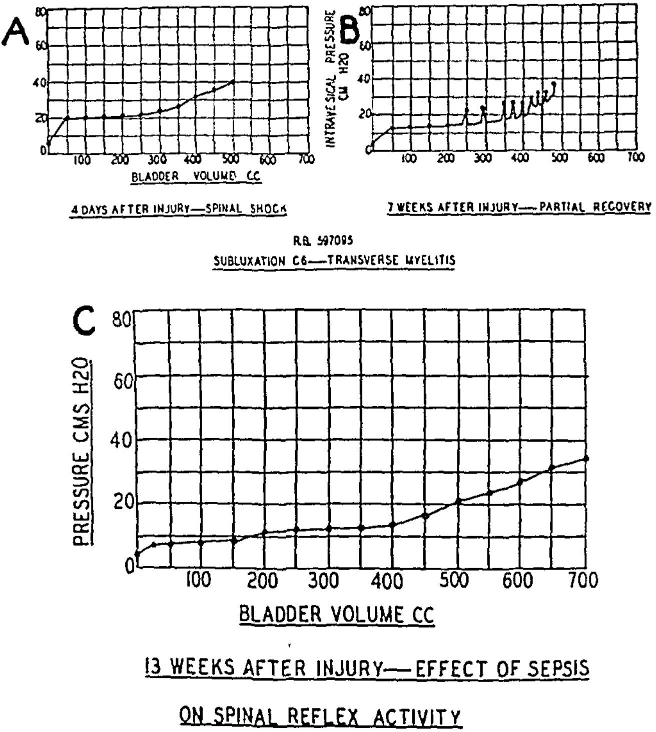
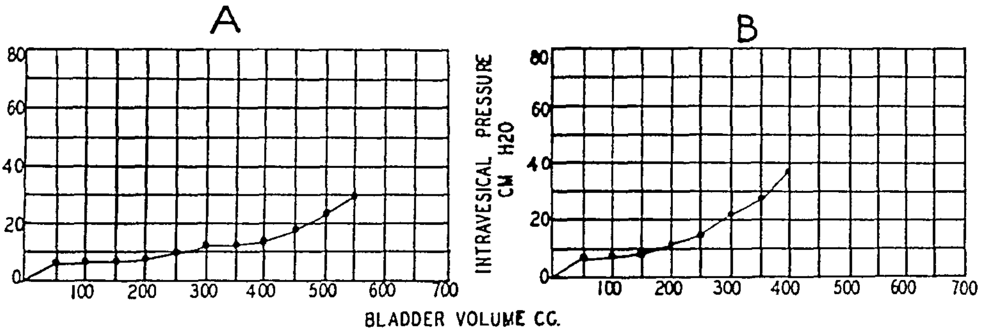

A
80
60
40
20
0
100
200
300
400
500
600
700
BLADDER VOLUME CC
4 DAYS AFTER INJURY—SPINAL SHOCK
B
INTRAVESICAL PRESSURE CM H20
7 WEEKS AFTER INJURY—PARTIAL RECOVERY
R.B. 597095
SUBLUXATION C6—TRANSVERSE MYELITIS
C
PRESSURE CMS H20
BLADDER VOLUME CC
13 WEEKS AFTER INJURY—EFFECT OF SEPSIS
ON SPINAL REFLEX ACTIVITY

Fig. 4

A cystometrograph was then obtained; this is illustrated in figure 3, *C*. Figure 3, *D* demonstrates the bladder reaction 2 hours after spinal transection. It will be observed that the cystometrographs are exactly the same as those obtained while the animal was under the influence of spinal anesthesia. The tone of the detrusor as well as its ability to maintain an approximately constant intravesical pressure with varying volumes of fluid was not altered.

Figure 4 demonstrates the cystometrographs of the bladder of a 46 year old patient who fell 40 feet from the top of an embankment and sustained a subluxation of the cervical spine at the junction of C6 and C7 with an apparent compression fracture of the body of C7. Physical examination disclosed a complete flaccid paralysis from the level of the shoulders caudad. Respiration was entirely diaphragmatic in type. Shortly after the diagnosis was made, the patient was placed in ice-tong traction and on continuous inlying urethral catheter drainage. Cystometric examination (fig. 4, *A*) was performed 4 days after the initial injury. It will be noted that bladder tone and accommodation are normal in appearance. The voiding contraction is absent. Seven weeks after injury the bladder, coincident with the appearance of skeletal reflexes, began to demonstrate a response to segmental reflex activity as indicated by the small uninhibited contractions in figure 4, *B*. These contractions, as well as skeletal reflex activity disappeared at the end of the thirteenth week after injury (fig. 4, *C*). It is believed that the disappearance of activity in the severed spinal cord was due to the generalized sepsis and pyrexia produced in the patient by large infected bedsores. This opinion is in accord with the observations of Head and Riddoch[11], who stated that "attacks of septicemia, whatever the origin, greatly delay the establishment of automatic micturition and that all febrile conditions tend to diminish the responsive power of the spinal cord."



7 HOURS AFTER INJURY—SPINAL SHOCK

5 WEEKS AFTER INJURY

H.L. 549329

COMPRESSION FRACTURE L1—TRANSVERSE MYELITIS

FIG. 5

The cystometrograph in figure 5, *A* was obtained 7 hours after the onset of spinal shock in a 60 year old carpenter who fell from the roof of a building and received a compression fracture of the first lumbar vertebra. Again it can be seen from the cystometric examination that bladder tone and accommodation are within normal limits. In figure 5, *B* it can be observed that reflex activity had not returned 5 weeks after injury. Four other patients in spinal shock following acute injury to the cord were recently observed. Cystometrographs were performed shortly after their admission to the hospital. No alterations in bladder tonus or accommodation were noted in any of the patients.

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[11] Cobb, S. and Wolff, H. G.: Archives of Neurol. and Psychiat., **28**: 661, 1932.

DISCUSSION

It is well to interpret the term "tonus" before further discussion is attempted. Cobb and Wolff[11] in a review article on the tonus of skeletal muscle, made a plea that the term "tone" be discarded insofar as the description of the state of tension in striated muscle is concerned. It was suggested that more specific terms as "standing reflex," "postural reflex" and "righting reflex" be substituted for the term "tone." The development of tension in striated muscle is independent of voluntary innervation but *dependent upon stimuli of some type coming to the muscle from the central nervous system: it is a reflex phenomenon.* If the nerve going to one of the skeletal muscles is cut, the muscle elongates and becomes flaccid. This flaccidity and loss of tension in striated muscle is observed in the first stage of acute spinal cord injury which is characterized by the loss of spinal reflexes and vaguely termed spinal "shock."

It has been commonly observed that smooth muscle will maintain much of its tension or resistance to extension under conditions of complete denervation. Some smooth muscle will even exhibit rhythmic contractions under the above conditions. These characteristics are utilized in differentiating between skeletal and plain muscle[12]. It is thus quite difficult to visualize the state of flaccidity or atonicity occurring in bladders of patients suffering from acute spinal cord injury, since one of the properties of smooth muscle is to maintain its tonus despite loss of the spinal reflexes or its extrinsic nerves. Some workers[13] believe that the higher centers play a role in determining the tonus of the detrusor muscle. The present authors[7] have demonstrated that chemical blockade of the autonomic ganglia did not decrease bladder tone or the ability of the bladder to accommodate to increasing volumes of fluid at the same intravesical pressure although the voiding contractions were abolished. Further observations in the present investigation have demonstrated that spinal anesthesia and spinal "shock" produced no essential change in tonicity or accommodation of the detrusor muscle although there was a complete absence of any voiding contraction. *From the above observations it would appear that normally there are no tonic efferent discharges being mediated by the parasympathetic nerves which are the only motor supply to the detrusor muscle.* It is believed that the lower motor neurons (at the level of sacral spinal segments 2, 3, and 4) send their discharges down the pelvic nerve only for the purpose of initiating and maintaining the emptying contraction of the bladder. Normally the lower motor neurons are inhibited

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[12] Evans, C. L.: Physiol. Rev., 6: 358, 1926.

[13] Langworthy, O. R., Kolb, L. C. and Lewis, L. G.: Physiology of Micturition. Baltimore: Williams & Wilkins Co., 1940.

from discharging impulses by the cortico-spinal tracts which are under voluntary control. When the bladder is filled to that capacity which creates the desire to micturate, the individual releases the inhibition and permits the lower segmental reflex to be activated thus resulting in a voiding contraction of the bladder. If there is a lesion of the pyramidal system, then there will be uncontrolled or uninhibited contractions of the detrusor. The contractions vary in magnitude depending upon the number of afferent stimuli activating the lower motor neurons.

It is believed that the term "tone" should be confined to that condition of tension in the detrusor which exists independently of central nervous system connections. Further increases in tension produced by impulses coming from the central nervous system should be designated as the "voiding reflex." The term "atonic bladder" should not be used to describe a bladder which cannot be emptied voluntarily but should be utilized to designate bladder muscle demonstrating a marked decrease in tension. Atonicity obtains in bladders that are permitted to distend abnormally over a varying period of time. Thus, distension may occur with a) loss of sensation as in patients with tabes dorsalis, b) obstruction as in patients with vesical neck contracture or prostatic hypertrophy, or c) loss of the entire segmental reflex arc involved in the act of micturition as in spinal "shock." Muellner[10] has demonstrated that bladder tone is decreased during pregnancy and is on a chemical rather than on a mechanical basis.

The few observations recorded in this paper tend to suggest that bladder tonus is normal during the period of spinal "shock" provided that retention of urine with distension is not allowed to take place.

CONCLUSIONS

It is suggested that the urinary bladder muscle maintains its normal tone as well as the ability to accommodate to increasing volumes of fluid at approximately the same intravesical pressure, in the condition of spinal "shock."

It is probable that the atonic bladder observed in many cases of spinal "shock" is due to retention of urine with over-distension over a varying period of time, rather than being due primarily to the loss of the segmental reflex arc concerned with micturition.

NOTE: After this paper was submitted for publication further experiments, involving tonicity measurements of human and dog bladders immediately after surgical extirpation, demonstrated detrusor tone to be essentially normal.

THE RENAL MANIFESTATIONS OF PERIARTERITIS NODOSA[1]

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Periarteritis nodosa is a necrotizing vascular disease affecting medium sized and small arteries and arterioles. Its clinical manifestations are varied, and quite often of a bizarre nature. This disease usually involves the arteries of several organs, but it may be limited to one. The kidneys are most frequently affected, in 80 per cent of cases, according to Boyd, Herbut, Rolnick, and others. Usually renal involvement is associated with injury to other organs, but the disease may be limited to the kidneys, and rarely to one kidney.

The etiology of periarteritis nodosa is as yet unproven, although experimental as well as clinical observations suggest that it is probably a manifestation of hyperergy. Selye and Pentz mentioned the close relationship between this disease, renal hypertension, and rheumatic allergic manifestations. The literature contains many cases occurring in individuals with rheumatic fever, and others with bronchial asthma.

Lichtenstein and Fox report a case that was apparently due to sulfathiazole, and mentioned that similar vascular lesions have been reported following the administration of iodine, phenobarbital and thiouracil.

Rich reports 8 cases that developed [illegible] rapidly in individuals under treatment, and concluded that the vascular lesions are probably a manifestation of the anaphylactic type of hypersensitiveness. Five of his cases (4 with pneumonia and 1 with meningitis) received antiserum plus a sulfonamide. One case of meningitis received antiserum alone. Two surgical cases received sulfathiazole as a prophylactic measure. Experimentally he was able to produce periarteritis nodosa in rabbits by the use of horse serum. Using sulfonamides, however, he was able to produce a type of glomerular nephritis but not periarteritis nodosa.

Klinge, by repeated injections of horse serum in rabbits, produced a condition similar to rheumatic arthritis and noted an accompanying arterial lesion that closely resembled periarteritis nodosa. Marine and Bauman, by continuous feeding of thiouracil (½ and 1 per cent) to 103 rats found that 3 of this number developed periarteritis nodosa.

Selye and Pentz injected desoxycorticosterone acetate (DCA) in unilaterally nephrectomized rats fed a diet high in sodium chloride and were able to produce nephrosclerosis with hypertension, as well as lesions similar to those seen in periarteritis nodosa, thrombo-angiitis obliterans, and rheumatic fever.

Smith, Zeek and McGuire found periarteritis nodosa in 26 of 62 rats, and 1 of 8 dogs, which had been made hypertensive by wrapping their kidneys with silk. The animals developing the disease showed higher mean blood pressure levels, and, also, had more suppuration around the kidneys. In later experiments typical lesions occurred in the majority of cases of unilaterally nephrectomized rats, in which silk around the remaining kidney was infected with staphylococci or salmonella, or silk that had been rubbed on the floor. No such lesions were found in those in which silk similarly infected was wrapped around the spleen, or in those in which one kidney was left undisturbed, or in those in which silk or infectious agents, or both, were introduced into the peritoneal cavity distal to the kidneys.

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[1] Read at annual meeting, Southeastern Section, American Urological Association, Palm Beach, Fla., March 29, 1947.

The lesions in periarteritis may be roughly divided into acute, sub-acute and chronic phases. Frequently all three are demonstrable in the same organ. First occurs necrosis of the vessel wall, usually beginning in the media and subintimal layer. This may be followed by rupture and hemorrhage, thrombosis with infarction, or aneurysmal dilatation. The end stage is fibrosis and nodular thickening of the arterial wall and surrounding tissue.

The patient may present one or several symptoms. However, in classical cases the tetrad of symptoms of 1) polymyositis or polyneuritis, 2) episodes of abdominal pain, 3) weakness and anemia, and 4) nephritis, are suggestive. Few cases are diagnosed antemortem. In a small percentage superficial nodes appear underneath the skin and are accessible for biopsy. In suspected cases muscle biopsy may establish a diagnosis. Acute involvement of various organs, such as the appendix, gallbladder, or kidney, has led to surgical intervention. In a series of 168 cases collected by Boyd, 21 were subjected to laporotomy during the early stage of their illness.

The relative frequency of urinary symptoms has been noted by many observers. Four of 5 cases reported by Branowitch had hematuria. Logue and Mullins, in a review of 177 cases, listed hematuria as one of the symptoms in 48 per cent. According to Spaulding, hematuria may be unilateral, suggesting renal tumor. Several cases of hemorrhage into the perirenal space causing severe pain suggestive of renal colic have been reported. Hardeman reports a case of massive bilateral perirenal hemorrhage. Renal infarcts due to thrombosis is not uncommon. Hematuria is often associated with pain in the region of one kidney according to Rolnick. Boyd suggests that some cases of so-called "essential hematuria" may be due to this disease.

During some stage of the disease the urine will almost invariably show albumin and casts, and very often red and white blood cells. These abnormalities of the urine may be present early when other clinical evidence of nephritis is absent. Failure of renal function with death from uremia is common.

Hypertension is a common finding, being present in over 58 per cent of reported cases. Its sudden development during an obscure illness is suggestive. The clinical picture of nephrosclerosis is frequently presented in periarteritis nodosa, and some believe there is an intimate relationship between the two diseases.

Apparently the diseases causing hypertension of renal origin may be grouped into two classes: Those affecting the renal artery, or its orifice, thereby causing narrowing of the lumen and renal ischemia; and those in which the disease affects primarily the renal parenchyma. The reported causes of the former include arteriosclerosis, congenital displaced plug of smooth muscle, dissecting aneurysm and thrombosis of the renal artery, and periarteritis nodosa.

The following cases were chosen for presentation because in each case the history was suggestive of urinary tract disease. Periarteritis cannot be diagnosed from the urinary findings alone, but with its frequent renal involvement, it should be borne in mind as it may easily simulate common urological diseases.

CASE REPORTS

Case 1. No. 435820. A 38 year old white oil field worker was admitted to the hospital December 31, 1942, complaining of pain in the right side, which radiated to the corresponding testicle and down the inside of his right thigh. This was accompanied by nausea but no vomiting. Five weeks previously he had experienced a similar pain in his left flank, which also radiated to the left testicle. His local physician suspected renal colic due to stone and ordered hospitalization. He was admitted to another hospital where the following findings were recorded: Blood pressure 128/80, temperature 100.4, pulse 70, respiration 20. The blood showed a red cell count of 4,620,000, 90 per cent hemoglobin, and the white cell count of 17,000, with 85 neutrophiles. Urinalysis revealed specific gravity of 1.030, one plus albumin, a few hyaline and granular casts, 10 to 15 erythrocytes per high power field. Radiographic examination, including excretory urogram, failed to demonstrate the presence of stones, and showed very good renal function. During his stay there the temperature ranged from 99 to 101 degrees.

He was discharged on the fourth day and returned to his home. Between this episode and the present onset with pain in his right side, he has experienced backache, joint pains, and headaches. He also noticed that his urine was red on numerous occasions, and thinks he has passed some gravel in his urine. His appetite had been poor, and there had been some nausea and vomiting. He had also had some shortness of breath with slight chest pains, but no cough or hemoptysis. During this time he also had noticed that his eyes were swollen.

The patient had had numerous physical examinations during the past few years in moving from job to job and had always been told that his heart and blood pressure were normal. He was a patient in this hospital in 1939 at which time herniоplasty was performed for a left inguinal hernia. At that time his blood pressure was recorded as 120/78. The patient and his relatives suspected lead poisoning as a cause of his present illness, as his occupation had caused him to be exposed to lead fumes.

Physical examination showed a moderately ill, middle aged man with puffy eyes, *and bilateral shotty inguinal lymph nodes. Temperature was 99.2*, pulse 90, respiration 20. The blood pressure was now 180/110. Dental hygiene was poor, and the alveolar margin of the teeth and gums showed a definite blue line. The lungs were negative. The heart was apparently not enlarged at this time, but auscultation revealed a loud popping A_2. Examination of the abdomen, reflexes and extremities were negative.

The blood showed a negative Kahn, leucocyte count of *10,800* with 70 neutrophiles. The red cell count was 4,740,000 with 14 gm. hemoglobin. Blood smears were searched for stippling of the red cells, and only one cell could be found showing this change. The nonprotein nitrogen was 47.2 mg. per cent. The urine showed a specific gravity of 1.010, and 2 plus albumin, but was otherwise negative. The phenolsulphonphthalein test showed 25 per cent, 5 per cent, 5 per cent, and 2½ per cent excretion for fractions 1, 2, 3, and 4 respectively, total 37.5 per cent. Acid fast stains of the urine were negative.

An x-ray film showed the left kidney to be essentially normal in size and position, but the right appeared to be smaller than normal. The left measured about 5 inches in length against about 3½ inches in length for the right. No stones were evident. Cystoscopy revealed a normal bladder mucosa. Both ureters were easily catheterized, and no residual noted in either pelvis. An intravenous injection of indigo carmine appeared in 4½ minutes from the right side, with good concentration, and 5 ½minutes from the left side, with fair concentration. Retrograde pyelogram (fig. 1) showed clubbing of the calyces with calyectasis of a fair degree in the superior calyx of each kidney. There was narrowing of some infundibula suggestive of cicatricial changes. Radiographic examination of the chest showed increased lung markings in both hilar and perihilar zones with the left hilar zone enlarged. The cardiac silhouette was hypertensive in contour with a very prominent aortic knob. Ophthalmoscopic examination showed papilledema and other changes suggestive of the usual findings in malignant hypertension.

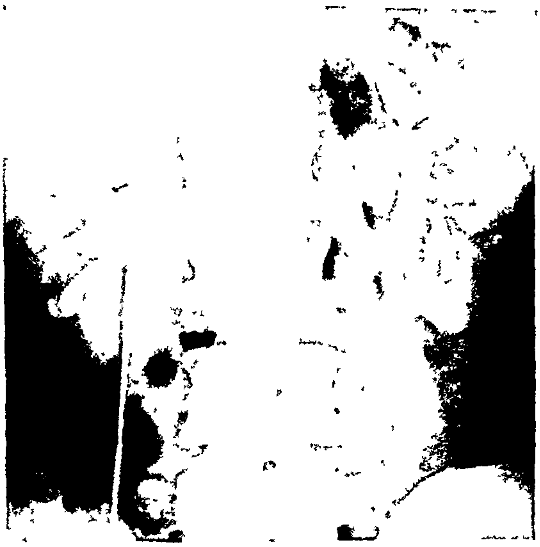

FIG. 1

During the period of hospitalization his course was progressively down hill. His blood pressure steadily rose, being 204/178 on the twenty-third day. Headache was constant, and he complained of pains in various joints and muscles. On the twenty-fourth day he was allowed to go home as unimproved, but was readmitted 3 days later in convulsion. At this time his blood pressure was 232/114. His heart was enlarged 2 cm. to the left of the Mcl, but there were no murmurs. The urine showed a specific gravity of 1.005, but otherwise negative. The nonprotein nitrogen on this admission was 26.8 mg. per cent.

Spinal puncture revealed xanthochromic fluid under 575 mm. of pressure (H_2O). The fluid contained 925 leucocytes, with 94 per cent polys, 8, 750 red cells, and 310 mg. per cent total protein. During the last few days there were numerous convulsive seizures, each one lasting about 3 minutes. His temperature throughout his hospital stay had been essentially normal, but ranged from 100.2 to 101.8 the last few days. He expired on the thirty-fifth day in coma.

Autopsy revealed undernourishment and hemorrhage measuring 2 cm. in width in the musculature along the right costal margin. The right and left lungs weighed 500 and 400 gm. respectively, and showed dependent congestion and a small area of consolidation in the right lower lobe. The heart weighed 400 gm. and the base of the left ventricle measured 2 cm. in thickness. The myocardium was firm and free from gross scars or nodules. The valvular and mural endocardium appeared normal. The right coronary ostium was located 1½ cm. above the level of the aortic valve. Both coronary ostia were fully patent and the major branches of the coronary arterial system were negative except for an occasional small atheroma Minimal arteriosclerosis was present in the aorta. The peritoneum was dry, grayish pink and free from adhesions. The mesenteric veins were engorged with concentrated blood. No gross lesions were detectable in the mesenteric, gastric, splenic and hepatic arteries. The congested liver weighed 1700 gm The spleen weighed 120 gm. and showed dark red, firm cut surfaces The left kidney weighed 130 gm. and showed an old infarct near the lower pole that had produced a deep fissure-like retraction. Elsewhere the surface was moderately nodular Surfaces made by section revealed essentially normal architectural features except in the region of the infarction. Aneurysmal dilations were present in both main branches of the renal artery, the lowermost measuring 1½ cm. in length and containing a dark red clot. The right kidney weighed 120 gm. The artery to the upper half was dilated and thrombosed, which was related to a recent infarct near the upper pole. A saccular aneurysm had formed in the proximal portion of the branch to the lower half of the organ and occupied a position that allowed partial compression of the main artery (fig. 2). The brain weighed 1510 gm. and showed flattening of the convolutions and congestion of the meninges. There was no thickening or milkiness of the meninges, and no gross lesions of the arterial system could be detected. Hemorrhage involved the right parietal and occipital lobes that had perforated the posterior horn of the corresponding lateral ventricle. The esophagus, stomach, intestines, gallbladder, extra-hepatic bile ducts, pancreas, adrenals, urinary bladder, prostate and lymph nodes showed no noteworthy change.

Microscopically, lesions characteristic of periarteritis nodosa were found in the brain, muscles of chest wall (only muscle examined), liver, renal arteries and kidneys. In the brain the vascular change was both recent and reasonably remote in development. In the former fibrinoid necrosis of the media associated with a cellular inflammatory reaction and sometimes thrombosis was observed. In older lesions the wall of the artery was thickened by chronic productive reaction, producing almost complete occlusion of the lumen. The adventitial zone was sparsely infiltrated by plasma cells and lymphocytes. In the muscle the lesions varied somewhat as to age but those observed were in the healing stage. There was marked fibrous thickening of the walls of the arteries with involvement of all layers. The reaction was fibroblastic in character in some, while in older lesions the thickened walls resembled more dense scar tissue. The vascular lumens were narrowed even to occlusion, the latter occasionally due to an organized thrombus. A few lymphocytes and plasma cells were noted in the perivascular zone in a few instances. It was assumed that the muscular hemorrhage developed through rupture of a vessel or vessels more recently involved, but this mechanism was not demonstrated in the sections available. The change in the liver consisted of marked fibrous thickening of an occasional artery in the subcapsular zone, which reduced the lumens to mere slits that were sometimes eccentrically located. In the kidneys the vascular change was of two types. Moderate hyperplastic change and less frequently necrosis was more or less diffusely present in the arterioles. This was not conspicuous and might be overlooked on cursory examination. The interlobular arteries were spared this change. The other type of lesion was characteristic of periarteritis nodosa and occurred in small arteries including those of the order of the interlobular arteries (fig. 3). All zones of the affected arteries were thickened by fibrous tissue which varied from a dense hyaline to a more cellular character. In some instances the thickness of the wall of the artery was not uniform, but segments were thicker and more fibroblastic than elsewhere and produced bulgings into the narrowed lumens.

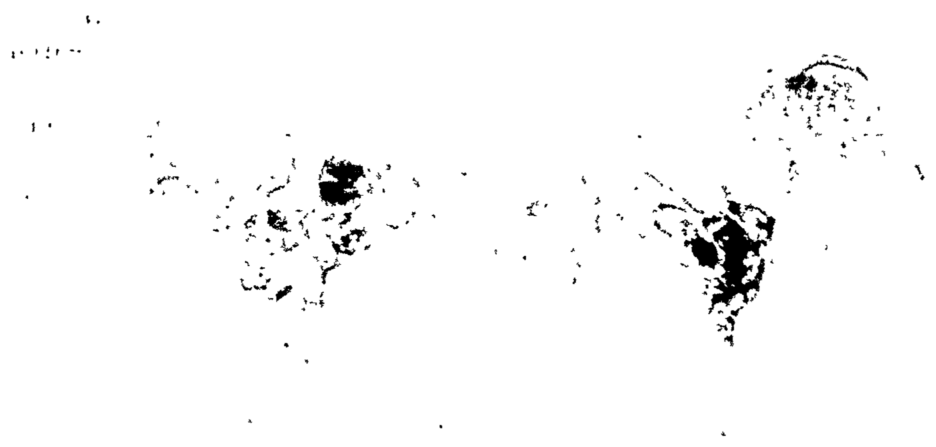

FIG. 2

Case 2. No. 73043A. A white female, aged 53, married and the mother of several children, was admitted with the complaint of pain and a lump in her left flank.

Two months ago the patient began to notice a dull aching pain in her left side, which had steadily progressed. Two weeks before admission she became aware of a mass in her left side, which caused a dragging sensation, more noticeable at night. She seemed to feel better while up and around, but for the past 2 weeks she had felt herself growing weaker. There had been no hematuria or painful urination. About 9 months ago she began having generalized aches and pains, and did not feel well. Six months ago she had all of her teeth extracted on the advice of her physician.

Physical examination was negative, except for a large, smooth, tender mass lying in the left upper quadrant and extending to the crest of the ilium. Her blood pressure was 132/84. Urinalysis showed specific gravity of 1.018, one plus albumin, 20 to 30 red blood cells, and 10 to 15 white blood cells per high power field. Examination of the blood showed a total of 3,440,000 red blood cells with 10 gm. of hemoglobin. The leucocyte count was 7,950 with 78 neutrophiles, 17 small lymphocytes, 8 large lymphocytes, 1 eosinophile. Bleeding time was 1 minute and 15 seconds, and coagulation time was 2 minutes and 30 seconds. A plain film showed the right kidney to be in normal position, and apparently normal size, while the left kidney shadow appeared to be quite large No stones were evident Excretory urogram (fig. 4, A) showed what appeared to be a normal pelvis and calyces on the right side, but no dye appeared in the left kidney at the end of 15 minutes. Cystoscopy showed mild cystitis, the bladder being otherwise normal. The left ureter was catheterized easily and 15 cc of urine aspirated from the left pelvis. Retrograde pyelogram (fig. 4, *B*)

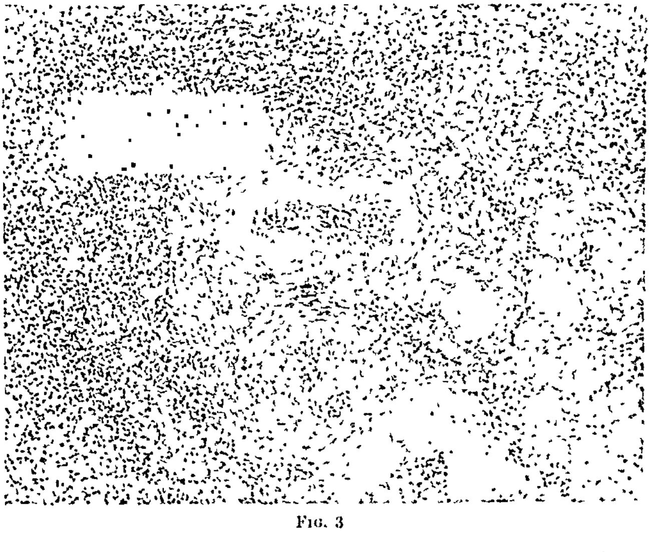

FIG. 3

showed ureterectasis, pyelectasis, and calyectasis of the upper and middle calyces with apparent absence of the lower calyces. A diagnosis of tumor of the left kidney was entertained and hospitalization advised. The patient was admitted March 30, 1943.

On the next day the patient was prepared for left nephrectomy, after transfusion of 500 cc of whole blood. Through the usual lumbar incision the left renal fossa was opened. On opening the fatty capsule a quantity of old blood clots poured into the wound and this was followed immediately by profound hemorrhage of fresh blood. Efforts to control the hemorrhage with pressure and tamponade were unsuccessful. The kidney with its fatty capsule was rapidly delivered and clamps applied to the pedicle. The kidney itself presented a peculiar cyanotic appearance and had a peculiar consistency. In order to stop the hemorrhage, which was quite profuse, it was necessary to apply clamps lower and lower on the renal pedicle, and with the application of the last clamp bleeding ceased and the kidney was removed. In attempting to ligate the pedicle, it was then found that the bottom clamp included in its jaws the edge of the abdominal aorta at the point where the renal artery emerged. Efforts to suture the edge of the aorta were unsuccessful, so this clamp was left in place, the wound closed lightly around it, and the patient returned to her bed in a mild degree of shock.

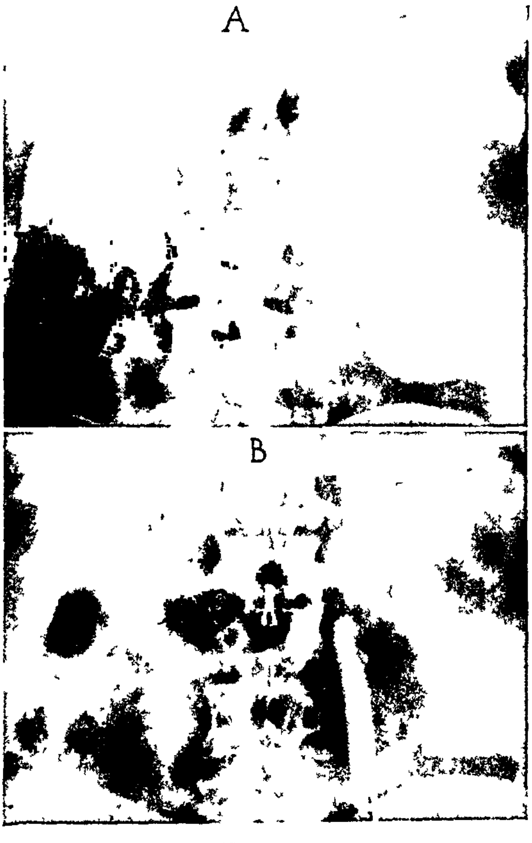

Fig. 4

The immediate postoperative convalescence was uneventful but the clamp was allowed to remain in place until the ninth postoperative day, at which time she was returned to surgery, and with a surgical consultant the wound was reopened and further efforts made to suture the aorta. These were unsuccessful, as each time the clamp was loosened fresh hemorrhage would occur. The wound was again closed around the clamp and the patient returned to her bed. On the eleventh postoperative day she was again returned to surgery and a transperitoneal attempt made to suture the aorta but this was also unsuccessful. On the twelfth postoperative day the clamp came away and the patient rapidly expired of hemorrhage. Permission for autopsy was refused.

Examination of the organ revealed it to be surrounded by a thick pad of fat that had been dissected from its attachment to the capsule by a spreading hemorrhage. This latter was indicated by the presence of clotted blood on the surface of the kidney as well as on the apposing surface of the investing fatty layer. The kidney devoid of its fatty investment weighed 160 gm, and on section showed brownish red moist surfaces exhibiting fairly distinct architectural features. The pelvis was a little dilated, contained blood and showed a smooth, red lining. The peripelvic tissue was hemorrhagic and showed small yellowish nodules that appeared to be related to small arteries in this location. However, a ruptured vessel or other source of the hemorrhage was not demonstrated. The portions of the branches of the main renal artery present were free from gross lesions.

Microscopically, quite marked change centered about the small and medium-sized arteries, especially in the peripelvic zone. In a number of sections including the subpelvic tissue arteries were encountered showing alteration considered characteristic of periarteritis nodosa. Chronic productive change involved all zones of the walls of the affected arteries but not uniformly so. The adventitia was regularly conspicuous due to fibroblastic reaction or to the presence of fibrosis of a denser character and was infiltrated by lymphocytes, plasma cells and sometimes a few polymorphonuclear leucocytes and eosinophiles. In the larger arteries of this location the media usually did not show uniform involvement, but it was more frequent to find fibroblastic proliferation involving the media for about one third or one half the distance around the lumen leaving the remainder little altered. This resulted in marked focal thickening and an asymmetrical appearance of the vessel (fig 5). Not infrequently the internal elastic lamina appeared essentially undisturbed for a part of its distribution, while the remainder in such a vessel was fragmented or not detectable. The condition of the elastic lamina could be correlated with the fibroblastic reaction in the media and intima which represented repair of the earlier process of fibrinoid necrosis. The presence or absence of the internal elastic lamina depended upon whether only the outer portion or the entire medial zone was involved. Where fibroblastic change involved the intima as well as the media the elastic lamina was either fragmented or missing. The perirenal hematoma showed organization which indicated hemorrhage of some duration.

Case 3. No. 163192. A colored male, aged 21, was admitted April 15, 1945 with a complaint of weakness, stomach trouble, and bloody urine. The patient's present illness began 1 month ago as a severe headache, which disappeared after 2 days. A few days later he began having pain and soreness in his right inguinal region, which seemed to spread over his lower abdomen. The pain was described as being of a griping character. This has been accompanied by nausea and vomiting, which seemed to occur about an hour after meals. Several days before admission he began passing bloody urine. Since the onset of his illness he had become very weak.

He had measles and chickenpox during childhood, pneumonia 5 years ago. Eight years ago he had a penile sore with an abscess in his left groin. For this he received 100 "arm" and 50 "hip" shots. Two years ago he had gonorrhea. He had coughed up blood on several occasions, and 4 years ago his nose bled for a day and a half. His mother died 1 year ago of a tumor. There was no family history of tuberculosis or kidney trouble.

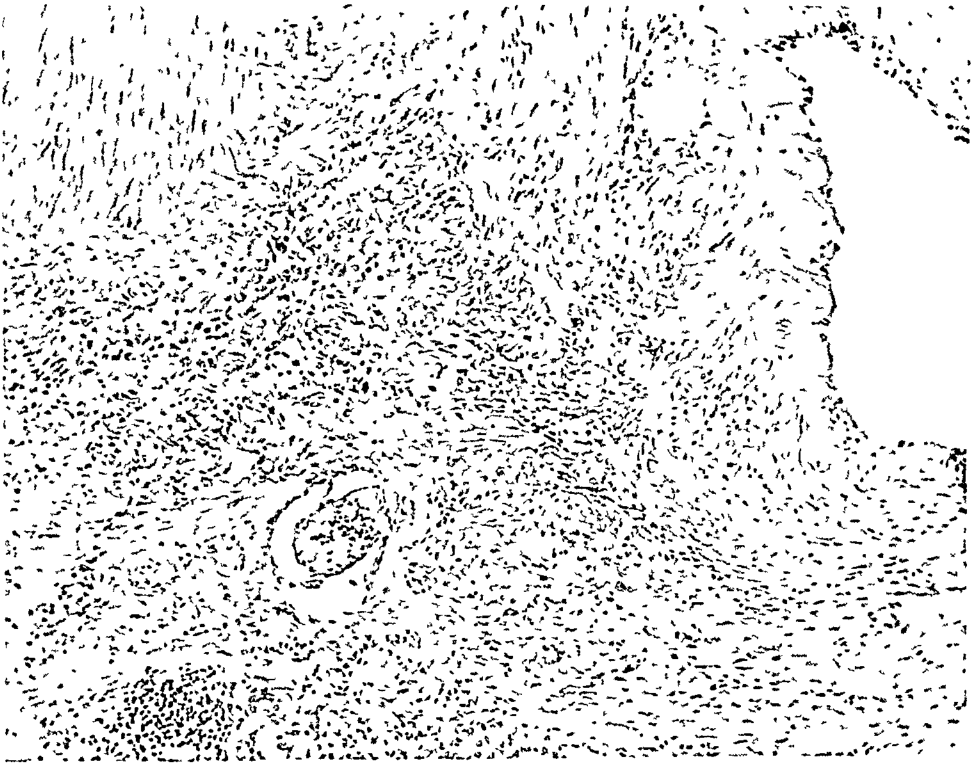

FIG. 5

Examination revealed a poorly developed and nourished colored male, who appeared to be chronically ill. His skin was dry, and there were peculiar brownish blotches over his shoulders, chest, and thighs. His eyes reacted to light and accommodation, and the sclera was jaundiced. Blood pressure was 246/170. His heart was enlarged, the PMI being in the sixth I. C. S., anterior axillary line. The rate and rhythm were regular and there was a loud systolic mitral murmur. His spleen was palpable, and there was tenderness in the lower part of the abdomen. On rectal examination a mass could be felt above the prostate gland that seemed to involve the periprostatic area. His reflexes were physiological.

Urinalysis showed specific gravity of 1.006, two plus albumin, a few large clumps of pus cells, and was grossly bloody. Sputum was negative for acid fast stains on 3 occasions. Blood examination showed a hemoglobin of 7 gm., and a leucocyte count of 4,800. The Kahn and Kline were negative. The non-protein nitrogen was 142.9 mg. per cent, creatinine 3.9 mg. per cent, and icteric index 5.9. His course in the hospital was steadily down hill, with fever ranging from 99.2 to 100 degrees, and he died apparently in uremia on the eleventh day.

At autopsy, undernourishment, wasting of the skeletal musculature and a white powdery deposit on the skin of the face, neck and shoulders were observed. The right lung showed basal adhesions, apical scarring and emphysema, and it weighed 500 gm. The left lung weighed 420 gm. Both organs showed dependent congestion and edema. The heart weighed 600 gm. and both ventricles appeared dilated. Chalky flecks, measuring 3–5 mm., were seen through the epicardium, on cut surfaces of the left ventricle (chiefly in its outer portion), and to a less extent on cut surfaces of the right ventricle. The valvular and mural endocardium showed no noteworthy change. The coronary ostia were normal, and the coronary arteries showed an occasional minute atheroma. A few small atheromata were noted in the aortic arch. The duodenal mucosa was congested and showed nodular thickenings, the summits of which appeared ulcerated. The lower jejunum showed segmental congestion and thickening without detectable ulceration of the mucosa. The lining of the ileum was diffusely congested, and this organ also showed segmental thickening and stiffening of its wall where a pseudodiphtheritic membrane and shallow ulcerations prevailed on the mucosal aspect and where fibrin appeared on the serosa. Congestion and shallow, elliptical-shaped ulcers, tending towards segmental distribution, were present throughout the colon. The mesenteric lymph nodes were not enlarged, and the mesenteric arteries showed no gross lesions. The spleen weighed 120 gm. The liver weighed 2000 gm. and presented a smooth non adherent capsular surface. The kidneys were approximately equal in size and had a combined weight of 240 gm. Their capsules stripped with some difficulty exposing granular red surfaces flecked with many flea-bitten hemorrhages. Surfaces made by section were mottled gray, yellow and red and showed indistinct cortical striations and cortico medullary demarkation. The small arteries were prominent. The peripelvic fat was increased bilaterally, and the right pelvis was slightly congested. The ureters appeared normal. The lining of the urinary bladder showed several dark red, slightly elevated areas that measured up to 0.7 cm. in diameter. In some instances these appeared to be superficially ulcerated. The seminal vesicles were scarred and unduly cystic. The prostate, esophagus, stomach, pancreas, gallbladder and adrenals showed no noteworthy change. The brain was negative except for edema and moderate arteriosclerosis.

Microscopically, acute lesions of periarteritis nodosa were observed in the duodenum, jejunum, (fig. 6, A), ileum, urinary bladder, prostate and pancreas. In the pancreas somewhat older lesions characterized by fibroblastic reaction

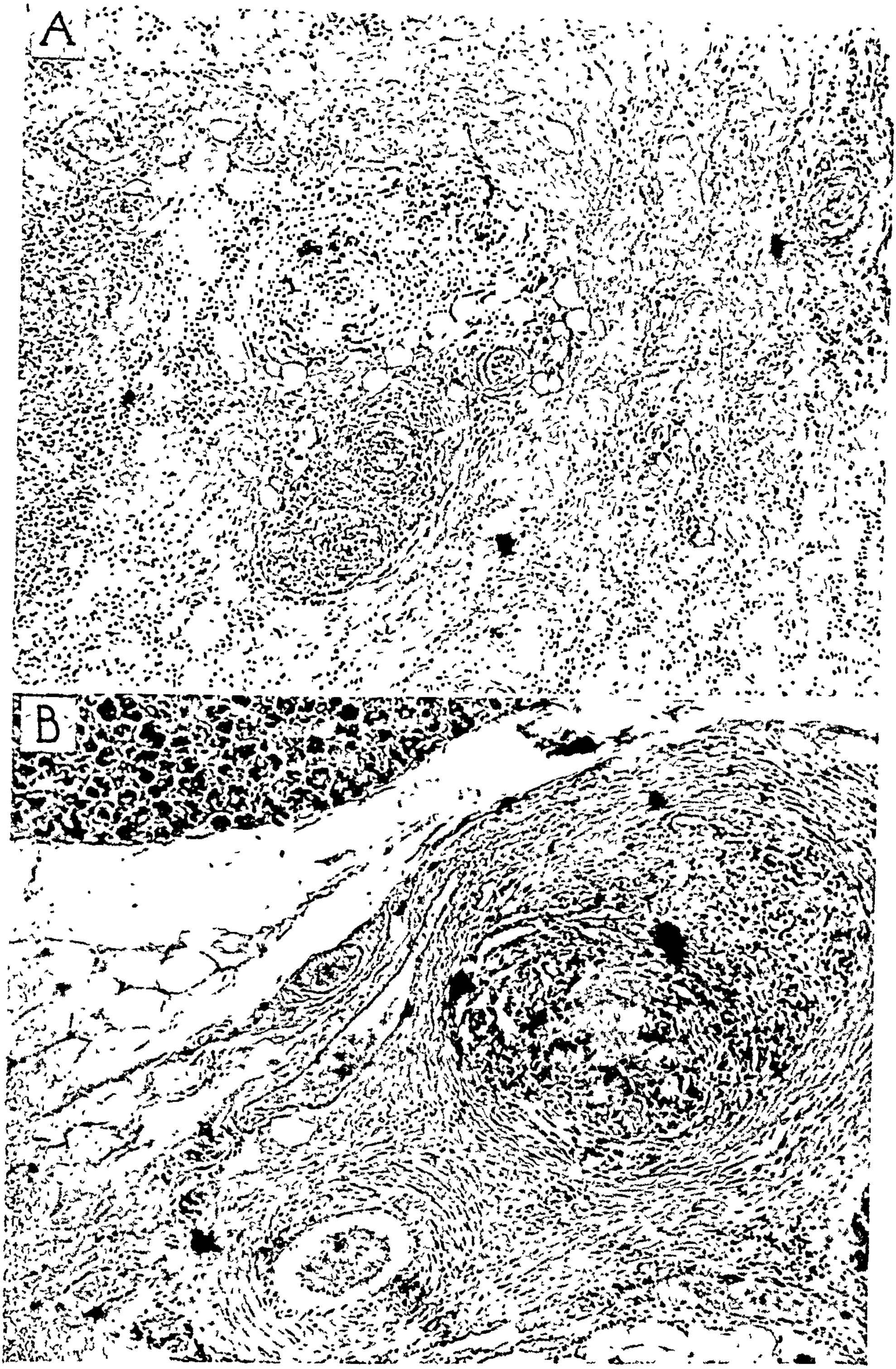

FIG. 6

were also encountered (fig. 6, *B*). In the kidneys the vascular change appeared to be uniformly characteristic of hyperplastic arteriolosclerosis, diffusely affecting the interlobular and smaller arteries and arterioles. Frequently the adventitial zone was formed by a broad mantle of dense fibrous tissue, but medial change characteristic of periarteritis nodosa was lacking, and the intimal proliferation and reduplication of the internal elastic lamina constituted the outstanding vascular alteration (fig. 7). Similar arteriolar change was observed in the liver, pancreas and adrenals. The kidneys additionally showed glomerular and other changes encountered in malignant nephrosclerosis. The heart showed hypertrophy and interstitial fibrosis but less microscopic evidence of degeneration than would appear to be commensurate with the prominence of the macroscopic manifestation of focal necrosis.

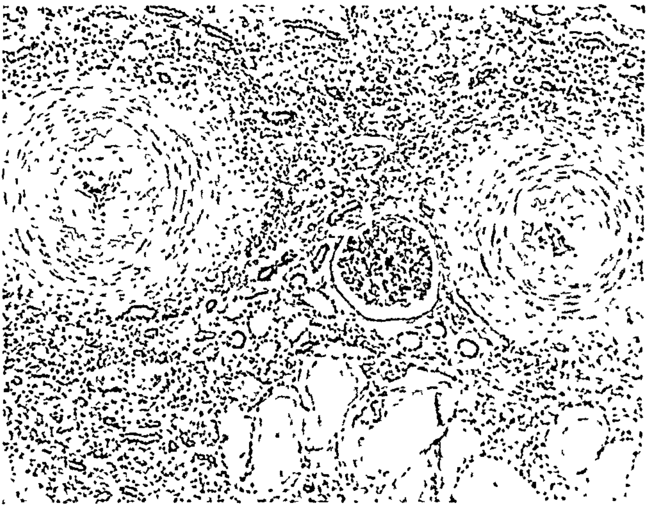

Fig. 7

DISCUSSION

Case 1. There was no hypertension in this case until 5 or 6 weeks before admission. All of the main renal branches were involved, 3 showing dilatation and partial thrombosis in some instances, and one showing a saccular aneurysm that partly compressed the main renal trunk. It seems clear that the hypertension is secondary to aneurysms of the branches of the renal arteries, and whether or not the compression of the main artery on the right by the aneurysm contributed would be problematical. In other words, there was sufficient reason for hypertension without invoking this latter mechanism. The early hyperplastic change of the arterioles appears to be secondary to hypertension due to the aneurysms of the renal arteries. Whether the vascular change characteristic of periarteritis present in the parenchyma contributed to the hypertension, or how much it contributed is problematical. This change in the sections available for study appeared to be focal and not very abundant. Since the history notes that this patient had exposure to lead fumes, one has to take lead poisoning into account as a cause of the hypertension. Some claim that lead may cause arteriosclerosis, hypertension and contracted kidneys. None of these manifestations, however, seem any more common in lead workers than in the average individual. One wonders if the patient did really have a lead line since the teeth were said to show the discoloration also. It is necessary to distinguish between lead line of the gingivae and staining of teeth that may be seen through the gums, appearing to be in them. Furthermore, the presence of a lead line does not mean that such a patient is suffering from lead poisoning. A lead line may persist for many years after exposure without symptoms of poisoning. The best clinical evidence against lead poisoning is the lack of basophilic stippling of the red cells. Only one could be found showing this change, which would not necessarily be abnormal for a normal person. The anatomic change observed at autopsy was that of periarteritis nodosa and not lead poisoning, although the slight diffuse arteriolosclerosis would have to be considered secondary to the effect of hypertension or something else. I would doubt that lead had anything to do with it. I think that we have to assume that periarteritis had something to do with the cerebral hemorrhage since lesions were found there, although such a mechanism (rupture of an affected vessel or aneurysm resulting from vascular damage) was not demonstrated. It would seem likely that both played a part in the hemorrhage.

Case 2. It is unfortunate that autopsy was unobtainable in this case. Undoubtedly she had been bleeding for sometime, at least 2 weeks. From her history she stated that she felt as though she was getting weaker day by day. We do not know the exact source of bleeding, but from the operative findings it was probably the renal artery itself. Tht extravasated blood was being held in check by the fatty capsule and when this was opened the tension was released and the hemorrhage promptly increased. It was evident that the source of bleeding was in or near the pedicle as it could only be controlled when clamps were applied, and, as stated before, the last or bottom clamp was the one which stopped the hemorrhage. Altogether 4 clamps were applied and it is quite possible that she did have an aneurysm of the renal artery which was crushed and obliterated by the clamps.

Case 3. There are no cystoscopic or pyelographic studies in this case, as it was readily apparent that he had some type of systemic disease, and also his condition deteriorated rapidly. So far as the kidney lesions are concerned, they are quite characteristic of malignant hypertension with uremia. There is no arterial change here that can be considered characteristic of periarteritis nodosa. He did have acute periarteritis of the pancreas, intestinal tract, prostate and urinary bladder. It seems likely that the hematuria came from mucosal ulcers and submucosal hemorrhages due to acute periarteritis nodosa of the bladder, although it is occasionally observed as a manifestation of malignant nephrosclerosis, which this man had. This case appears to be significant in view of the observation of Smith, Zeek and McGuire on experimental production of periarteritis in animals. Their data supported the hypothesis that periarteritis nodosa was associated with sharply rising hypertension and tended to refute the theory that the disease was due to hypersensitivity to antigens. I believe that we may assume that this patient had had at least relatively benign hypertension over a considerable period of time, perhaps several years. The marked enlargement of the heart would support this view. In patients whose hypertension has been malignant throughout its course or for most of its course, the heart does not reach great size. Actually they may die of their disease with the heart only slightly above normal weight. It is tempting to suspect that this case ran the course of benign hypertension (just how many years we do not know) until a month before entry when he developed severe headache. This appears to have marked the time when his hypertension transformed into the malignant type. The sharp rise in the blood pressure at this time could have caused the periarteritis nodosa. The age of the lesions would fit in quite well with the sequence. The abdominal pain, nausea and vomiting came after this event and would coincide as symptoms of periarteritis of the intestinal tract. *It is not surprising that he rapidly developed uremia, as rapid renal failure is the usual event in malignant hypertension of young subjects.*

SUMMARY AND CONCLUSIONS

Three cases of periarteritis nodosa that exhibited symptoms of urinary tract disease are presented and discussed in order to suggest that this disease is capable of being a pitfall to the urologist. One case of suspected nephrolithiasis, another of suspected renal tumor, and one admitted primarily because of profuse hematuria are reviewed. The established fact that periarteritis nodosa commonly involves the urinary system is re-emphasized.

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RENAL PEDICLE SYMPATHECTOMY[1]

E. GRANVILLE CRABTREE[2]

Section of the nerves of the renal pedicle and/or ureter for intractable pain of renal origin has had some vogue during more than 20 years. The operation has been done, both alone and in association with other surgery. It might be termed an operation of desperation for that small group of patients in whom degrees of pain far beyond toleration are encountered and due to which lives are ruined and drug addiction is common.

There is no doubt that, like renal suspension, renal pedicle sympathectomy has had a varied acceptance as a worthwhile procedure and has passed through periods of approval and condemnation, as is common during early employment of any procedure of limited usefulness. Where operations of this sort are introduced, a long time is often required for determination of the proper field of application. Eventually, it becomes possible for observers to collect recorded data on remote results, and go far toward establishing such operations in their proper perspective in relation to disease. The operation then assumes its rightful place in the armamentarium of surgery. Such deductions can be safely made only from compilation of long range results, (how does the procedure affect whole lives?) and not from determination of the condition of the patient at the time of discharge from hospital, or within a few months or a year after operation.

It is with the purpose of attempting to make some such estimate of the effects of renal pedicle sympathectomy that I present these few patients on whom the procedure was done years ago, together with the best available data obtainable throughout the intervening years.

Estimation of the usefulness of this operation must also include something of its peculiar occurrence as to type of patient in which intractable pain is encountered. A review of the literature shows such pain to occur wholly in women, and to occur during the menstrual stage of life. The patients are most often of high nervous temperament. There are often other causes for emotional disturbances in either personal, family, or economic affairs. The diagnosis of neurosis has been reported in almost all the patients. The duration of time under which these patients have been laboring under this diagnosis has often been long, covering several years in some who were cured of their complaints and led normal lives in subsequent years. Uncertainty on both diagnosis and result of operation is always a deterrent to surgery. To have a diagnosis of some other condition established after one has committed himself to a surgical procedure is at least disturbing. Such possibility is ever present in these patients.

Sufficient animal experimentation has been done to demonstrate the physiological condition of kidneys after renal pedicle denervation.

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[1] Read at annual meeting, Southeastern Section, American Urological Association, Palm Beach, Fla., March 28, 1947.

[2] Deceased.

Smith, in his book, *The Physiology of the Kidney* (1937), indicates that there is undoubted influence on change in blood flow through the kidneys, as a whole, and diuresis as two definite and consistent results of denervation. There may be some disturbance of the excretion of some solids but, at the time of his writing, these effects were not determined.

The kidney receives an abundant supply of sympathetic fibres by way of the thoracolumbar outflow and parasympathetic fibers by way of the vagus. Both sensory and motor endings are demonstrable in the renal structures. No main nerve trunks enter the kidney. Denervation consists of isolating and severing miniature fibres.

It has been demonstrated that the kidney can function without neural connections. A reimplanted kidney is adequate for maintenance of life for indefinite periods in animals.

From these considerations, any gain in relief of symptoms seems to be purchasable through this type of surgery, with little risk of functional damage to the kidney immediately following surgery or later on in life.

Clinical applications of denervation appear in American literature in 1921 through Eisendrath's translation of an article published by Papin and Ambard (Arch. des Mal. des Reins, 1: 1, 1921), and Papin's Guiteras Lecture in America, which appears not to have been published in English but appeared in French literature in 1931. Wharton and Hughson also reported in 1931 "a new operation," the data for which were read in January 1927, and one patient reported was operated on in 1924. Harris and Harris attempted an analysis of renal innervation and propounded the theory of the procedure of denervation. Since that time, Hess, Hepburn, Stone, Deming, and others have contributed by publication of cases or discussion. That Smith included data on the physiology of denervation of the kidney in experimental animals in his book, *The Physiology of the Kidney* (1937) indicated current interest.

My attempt to correlate the results of operation by others encountered difficulties, since in some instances operation had been aimed at the ureter, and in others at the renal pedicle. Furthermore, there had been so great a variety of types of disease included in the kidneys operated on, and the symptomatology for which operation was done was so varied that an impressive, but not too attractive list of indications for the procedure resulted.

Denervation of either the renal pedicle or the ureter has been recommended by the authors cited in the appended references and others noted but not included in the list for most of the symptoms commonly encountered in "painful women." It has had vogue in bilateral hydronephrosis and hydroureter, renal tuberculosis, early hydronephrosis, anurias, essential hematuria, gastro-intestinal disturbances due to dystopia, and some cases of parenchymatous nephritis, in addition to the cases of intractable renal pain with normal pyelography, save for evidences of pelvic and ureteral spasm.

Personal employment of sympathectomy has been limited to patients with intractable renal pain, without evidence of renal disease. It has been restricted to the renal pedicle on the grounds that there is evidence that surgical freeing of the kidney pelvis or of portions of the upper ureter is usually followed by some degree of atony of the ureter below the site of operation.

I have employed renal pedicle sympathectomy in 8 cases which were operated on between 1930 and 1946. It is with the purpose of establishing the end results in this small group of patients that this report is made.

A description of these 8 cases which comprise my entire surgical experience follows:

CASE REPORTS

Case 1. Miss H. S., a graduate nurse, aged 24, single, was seen in 1927. The presenting symptom was a series of chronic attacks of indigestion, which usually ended in spasms of pain referred to the right kidney, right upper quadrant, or general abdominal regions. Twelve years ago, appendectomy was done for indigestion, but the same symptoms persisted after operation. One and one-half years ago, gallbladder, one tube, and the left ovary were removed.

Six months later an operation was done for adhesions. Nine weeks after the gallbladder operation, pains in the right kidney became severe, and these were accompanied by bladder irritability. She soon began to have a low grade fever. There had been constant loss of weight and increasing sense of ill being throughout this whole 12 year period. Bladder symptoms appeared immediately after the gallbladder operation.

During the past summer (5 months) attacks of abdominal pain of rapidly increasing frequency and severity had occurred. These seemed to be of gallbladder type and led to exploration of the abdomen. Adhesions only were found. From then on, the pains were almost entirely renal in location, accompanied by bladder frequency. Pyelography elsewhere was negative.

When seen in the office, the patient complained of bladder symptoms which were constant with exacerbations and accompanied by nocturia of from 2 to 4 times each night. Attacks of renal pain occurred at least every day and were of from 4 hours to 16 hours' duration. The pain produced a feeling of tension, not severe colic, but was very severe. Occasionally, the patient had had 3 or 4 days of relief, but she soon got a "tuning up" feeling of local unrest after which a real attack set in.

There was doubtful tenderness of the right costovertebral angle. The kidney was not palpable. The urine was negative with no growth in culture, and guinea pig test showed no tuberculosis. Bladder cystoscopy showed no evidence of disease. Pelvic organs were not abnormal. The excretion of phenosulphonphthalein was 15 per cent in 15 minutes on the right side, the same as from the left kidney.

Pyelography showed normal kidneys and ureters, except that the right pelvis and ureter showed spasm.

Treatment by ureteral dilatation was carried out with a No. 10 bulb on 3 occasions in the next 3 months, without relief. During this time, the patient was away from work on vacation. Symptoms continued as before. She had gained 3 pounds, but felt no better than while working.

Re-examination by retrograde pyelography again showed a normally functioning kidney on the right side, but there was spasticity in pyelography as before. This time the calyces were a little dilated, probably from overdistention.

General examination showed long tubular type of chest; the diaphragm was low and its excursion was poor. The heart shadow was of the vertical type. There was quite a bit of hilus density and peribronchial fibrosis. There was no evidence of tuberculosis. Gastro-intestinal studies were negative for disease, although there was some ptosis.

All urinalyses were negative.

The blood picture showed nothing abnormal.

Renal pedicle sympathectomy was done in January 1930. The kidney appeared to be normal in all respects. There was marked peristalsis of both the ureter and pelvis at the time they were exposed in the wound. There were two aberrant arteries which entered the upper pole of the kidney. These were of such size that severance of them was not done. Only moderately thorough sympathectomy could be done because of vessel fixation of the kidney.

Convalescence was long. Bladder symptoms remained troublesome much longer than did renal pains and indigestion. By March 1930, the patient reported by letter that she "was feeling fine" and had done so except for the first month when her bladder distressed her.

In March 1931, fifteen months after operation, she reported that there had been but one attack of renal pain since operation, that she was working steadily, but remained thin. The attack of renal pain was accompanied by a temperature of 102° but she had had no medical care during the attack, beyond 2 injections of morphine during the acute stage of the pain.

In 1935 she was examined for general physical condition in Springfield, but her doctor made no mention in his notes of renal pain.

A Christmas card was received in 1939 which stated: "I am feeling fine and working every day, thanks to you who made this possible."

A final report by letter on January 18, 1947, states that there was complete relief for 3 years, after which the condition recurred but less severe symptoms accompanied it. Hysterectomy had been done in 1936, and since then she has been uncomfortable about twice a year. The attacks are longer, but less severe. I do not attempt to harmonize these conflicting reports.

Case 2. Mrs. E. C., a nurse aged 31, married, was seen in October 1930. A suspension of the right kidney had been done in 1928. The symptoms leading to operation were frequency, nausea and vomiting, dull pain in the right renal region, irregular and painful menstrual periods, and general unhappiness.

Following operation, she returned to hospital and was treated for urinary infection which was accompanied by nausea and vomiting, as before operation, fever, pain in right kidney, and swelling of one leg from time to time. She had been out of hospital for about 7 months. Her stay in hospital was two months long.

The symptoms on admission were continued dull pain in the right kidney, attacks of nausea and vomiting every few weeks, unable to lie on right side at night, and occasional swelling of the right leg. She weighed about 106 pounds.

The physical examination showed the right kidney was in the proper position and that it was not tender. There was evidence of loss of weight. The pelvic organs were negative to palpation. There was some evidence of abdominal ptosis. Blood pressure was low, 110/65.

The urine was infected with bacilli. There was a great deal of pus.

General complaints were dizziness, vomiting, nervous upsets occasioned by conditions of her work, swelling of legs at times, and almost constant pain in her left kidney region, which was dull and nagging in character.

The bladder capacity was 180 cc. The attacks of frequency were accompanied by general distress.

A girdle, provided for her by her physician, seemed to be intolerable.

She had pain in her right hip which was thought to be due to right sacroiliac disease.

During the following year, the urine was rendered sterile, but she had seen numerous specialists for numerous complaints. In general, there was no improvement in any of her complaints. Her gain in weight was but 7 pounds at her highest limit, and she soon lost that gain and more.

She was in the country during the summer, but there were constant series of recurring attacks of something or other about her person and she spent more time with her doctors than with her employer.

During several years she was known to have had a low basal metabolism. Her physician administered thyroid products. There was no appreciable improvement in any of her symptoms, and the renal pain remained paramount as an irritating factor in her poor health.

She was admitted to hospital in February 1930. Aside from some anemia and evidence of loss of weight, she showed no abnormal findings in physical examination, laboratory tests, or normal routine studies.

X-rays showed the following: Plain films of the urinary tract showed no stones or soft tissue shadows of note. Intravenous pyelography was negative. Since the pain was referred to the left kidney, retrograde pyelography was done. It was negative.

X-rays of the sinuses were negative. The cella tursica was also negative. Complete gastro-intestinal studies were done. Slight ptosis and gastric residue were shown. Neither was considered to be important findings.

The sacroiliac joints were considered to be normal. The spine was negative.

Dental films were considered to be negative.

The bladder urine was negative, culture negative, and the final report on guinea pig inoculation was negative.

On cystoscopy the urethra and bladder were negative. Excretion of indigo carmine was within normal limits. Pyelography was considered to be negative.

Renal pedicle sympathectomy was done on the left kidney.

The following year was hectic, from an emotional point of view. It was a great deal to expect that the years of illness could be wiped from the calendar of her thoughts easily. Her mental state was not improved when she fell into the hands of a clinican who left her with the impression that she had renal tuberculosis, had probably passed a stone, stone might recur, and that there was a bunch in her urethra which might be tumor. This all appeared to have been based on the past symptoms. Because of the state of apprehension present, the patient was re-admitted to hospital and thoroughly studied again. No disease was demonstrated.

Cystoscopic studies 1 year after operation showed the following: The bladder urine was clear, negative on examination, showed no tuberculosis by guinea pig inoculation, and was negative on culture. There was free flow of urine from each catheter. The urine was pale from the right side and more concentrated on the left. Appearance time on the right was 7 minutes with good density of color in 15 minutes. On the right side, the appearance of color was delayed 3 minutes more but the concentration of color was good.

Total phthalein excretion was 70 per cent in 1 hour from the bladder.

Bilateral pyelography showed what were considered to be normal pyelograms and ureterograms. Injection of the left pelvis to the point of distention, but not pyelovenous backflow, produced less discomfort than similar distention on the right side.

Three years later, the patient was seen in the office. The basal metabolic rate was minus 15. She was continuing on thyroid medications, felt better than for some years, and was doing full work as a nurse in a private family. There had been no recurrence of the renal pain since operation.

Twelve years later, there had been marked gain in weight; she had continued uniterruptedly at her occupation; yet, maintained a solicitude for health which continued to be a handicap except in those circles where discussions of health and hospital experiences have conversational value.

Case 3. Mrs. A. D., aged 46, married, was seen in December 1932. The past history was uneventful, save for three pregnancies without complications. There had been no operations. Catamenia was regular and her periods normal.

The present history began suddenly in May 1932. Her physician found her to have pyuria, which he cleared by medications. There was pain in the right kidney at that time and ever since, although the urine became free of infection. The pain was completely disqualifying.

Following the onset of pain, there began a series of examinations for numerous complaints which led to a variety of diagnoses. Her medical advisor made a diagnosis of gallbladder disease. Her surgeon considered her to have no gallbladder disease. Another medical consultant made the diagnosis of renal ptosis, or hydronephrosis, and still another a diagnosis of dilated colon. Her gynecologist found her pelvic organs negative.

There were, at no time, urinary symptoms.

The patient was a tall, thin woman who weighed 108 pounds. There was tenderness about the right kidney to deep palpation, but no mass, and the kidney was not ptosed. There was more tenderness in the region of the gallbladder than in the renal region. The urine was negative. The culture and guinea pig tests were negative. The Hinton test was negative.

Complete gallbladder and gastro-intestinal studies were made. These were negative. The blood pressure was 170/90.

Retrograde pyelography was done. The bladder showed no disease.

The right kidney appeared to be slightly larger than the left. There were no shadows suggesting stones. After injection, the right pelvis was a little large but showed no deformity. Both ureters were negative and appeared to be of normal calibre.

Renal sympathectomy was done in December 1932. There was nothing abnormal noted when the kidney was exposed.

Operation left the patient with a tender wound for some months. This gave pain but not of the character of her original pain, nor nearly so severe in type. She gained in weight from 103 to 168 pounds.

In 1936, she was taking thyroid extract on doctors orders, and her uterus had become enlarged from fibroid. Intravenous urography showed no changes in the urinary channels, and the function of the right kidney was similar to that of the left and within normal range.

In 1939, a divorce having intervened, she was re-examined when she brought her daughter in for examination. She no longer had pain about her wound, was still taking thyroid tablets, and was supporting herself by working as a buyer for a department store.

A final report, made by her physician in January 1947, states that the patient has become hypertensive, but she has had no significant kidney trouble since operation.

Case 4. Mrs. G. S., aged 34, married, was seen in March 1937. She had always been healthy until the first of 3 pregnancies 12 years ago, when she had pyelonephritis which persisted through the 2 subsequent pregnancies and was still present at examination. She had no treatment of her persistent urinary infection, but had very little in the way of symptoms suggesting it.

Four years ago, she began to have severe pain in the right kidney, for which cystoscopy and pyelography were done elsewhere. The findings were urinary infection and spasticity of the ureter on the right side, which was the seat of her pain. The ureter was dilated 6 or 7 times without relief of pain. There had been no treatment for 3 years.

During the 3 years without treatment, there continued to be pain in the region of the left kidney which was apt to have exacerbations lasting as long as 3 days. There was an ache at all times. The pain was frequent until she had had to remain in bed much of the time for the past 6 months. The fever usually disappeared at the termination of the acute attack of the pain.

The patient was a short, stocky woman. She had some pyorrhea. Considerable tenderness was elicited along the course of the ureter and about the left kidney, both anteriorly and posteriorly. Pelvic examination showed a lacerated cervix. There was some tenderness of the uterus on motion.

The urine was found to be hazy and showed a little pus; culture yielded 3 coli.

Cystoscopy showed a normal bladder, ureters, and urethra. The urine from the right kidney was negative, including culture. That from the left was hazy, showed small trace of albumin, and a few bacilli. The phenolsulphonphthalein test showed 20 per cent from the right and 20 per cent from the left side in 15 minutes.

Findings at this time were essentially negative, except for the history of almost unbearable pain. This pain was entirely referable to her lone left kidney. It was almost constant, very severe, and not related to anything in the normal course of living or her menstrual cycle.

The urine was entirely normal in all respects. She had been shown to be sensitive to diodrast, she reacted to adrenaline, and was free from obvious evidences of any other allergies.

Pyelographic and cystoscopic studies showed her to be normal except for a small ureteral orifice on the left.

X-ray studies showed her to have some calcified glands on the left side of the abdomen. The pyelography was entirely normal.

Renal function tests were within normal range.

General examination was negative for disease.

Paravertebral block of the ninth, tenth, and eleventh thoracic nerves brought immediate and complete relief of all symptoms. After a few hours, the pain returned with increased severity. This was done by Dr. Poppan of the Leahy Clinic.

After discussion of possibilities, it was decided that a joint operation by Dr. Poppan and me should be done. Dr. Poppan sectioned the above ganglia and I denervated the pedicle of the kidney. Markedly active peristalsis was obvious as in the other cases reported during surgery.

Convalescence was uneventful.

The immediate result was complete relief of pain on the same basis as was accomplished by injection. This relief has been permanent.

Dr. Leo Gibson of Syracuse, New York, had examined her for what he considered to be back strain. Pyelography was normal, and Dr. Gibson concluded that there was no reference of the pain to the kidney.

A Christmas card, 1946, reported all well. She has now reached a new height of accomplishment and is assistant professor of bacteriology in a well known school of nursing. A more full description of her state of health as of January 1947, indicated back strain for which braces are worn. In the judgment of her present physicians, the kidney plays no part in the present difficulties.

Case 6. Mrs. C. M., aged 40, married, was seen in November 1942. This patient introduced still another variation from the usual in this group of intractable pain patients in that her pain was always absent during the catamenia and pregnancy but returned after termination of either. This relationship is substantiated by the work of Saitz, who showed the influence of the catamenia, on the motility and calibre of the urinary tract. Surgery was not successful and may be considered to have brought out the fact that purely mechanical measures are not replacements for some other factors, like endocrines, about which less is known than about cutting procedures. Much remains to be done in endocrinology.

There had been pain in relation to the left kidney for 6 years. It was almost entirely disqualifying at times and periods of several weeks in bed had been repeatedly forced upon an ambitious woman. This pain was always entirely relieved by the onset of the catamenia. It was almost always present in the interim between periods. The pain was dull to very sharp in character. There were times when there was no relief from it, either when lying down or at work. The patient was clearly not a neurotic.

One pregnancy terminated 2 years ago. After the second month of pregnancy the pain entirely disappeared and she had a glorious time for the duration of pregnancy. As soon as the catamenia was established after delivery she began to have pains again.

Pain was entirely related to the left kidney. It consisted of a bad cramp which lasted for about 20 minutes and then eased off to reasonable comfort. There was never fever. Pains came as far apart as 2 weeks and then there were times when they occurred as often as 6 to 7 times a day. At those times, she had to remain in bed and was never free from pain. The bowels were always normal without catharsis. Catamenia was never troublesome.

Examination of the bowels by x-ray showed nothing abnormal. Blood pressure had been recorded elsewhere above 200 systolic. There had been a pre-eclamptic condition during her one pregnancy. The eyes were prominent. The thyroid was prominent. The pulse was 100 most of the time. A medical consultant considered her not to be a case of thyrotoxicosis. Blood pressure was 150/90. All urological data were negative for any form of disease which urologists recognize. The affected kidney showed a double pelvis, but no disease in either pelvis.

Denervation of the renal pedicle was done. The unusual findings were an aberrant artery on the posterior side of the kidney which was not situated at such a place as to embarrass the ureter or the pelvis. Otherwise, the kidney was entirely normal.

The end results were not good. There was no evidence that the operation had improved her condition, in any way. She was placed in the hands of an endocrinologist whose efforts were as unproductive of beneficial results as had been the surgery.

A future generation of endocrinologists will take on this type of patient and perhaps point with scorn to the procedures which have been employed with such unsatisfactory results.

Personal communication in January 1947, states that she has been in no way benefited by her operation.

Case 7. Miss K. G., aged 31, single, was seen in February 1941. She had always had excellent health until 3 years ago. At that time she had continuous right back pain, referred to the right groin. This led to removal of her gallbladder. During convalescence from that operation, she had 7 days of acute pyelonephritis.

A few months after operation, she had attacks of severe pains in the right side which came as frequently as every few days. The pain was said to have been accompanied by blood in some instances. Morphine seldom relieved the pain and she was etherized at times for it. She passed 3 calculi, all of which were recovered, but none analysed. Passage of the calculi did not give complete neg

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TESTIS TUMORS: REPORT ON 250 CASES[1]

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PATHOLOGY

Interpretation of the cellular structure of tumors of the testis requires not o experience with the microscopic pattern of carcinoma but also a working kno edge of embryological histology. The varied structure of testis tumors sugg that no one method of treatment would be adequate. Since 43 per cent of 250 patients had proven metastasis on admission to Walter Reed General H pital and in an additional 28 per cent metastasis eventually developed, it is ob vious that only a few could be cured by simple orchiectomy alone. Orchiectomy plus radiation therapy has proven satisfactory only in the case of seminoma. The apparent confusion in the classification of testis tumors has come about from the use of ill-defined terminology. As a result, many urologists have treated testis tumors by simple orchiectomy and radiation therapy because the results of radical orchiectomy without radiation therapy have not been satisfactory. Chevassu wrote: "A classification is not a catalog. It does not only register, it must explain." A clinico-pathological classification of testis tumors indicates that surgical treatment should be extended and radiation therapy rationalized.

Tumors of the supporting tissues of the testis, connective tissue and the blood vessels are similar to those produced in other parts of the body and will not be discussed here. No sarcomas or endotheliomas were seen in our patients of military age.

Specific endocrine tumors of the testis are composed of the interstitial cells of Leydig. Two or 0.8 per cent of our cases were interpreted as benign interstitial cell tumors, occurring in marvelously well developed men of 25 and 37 years. These tumors, while usually benign, may become malignant. Fresh tissue examination after section revealed reddish-brown solid tumors occupying the entire testis without gross evidence of remaining tubular elements. The tumors consisted of proliferating interstitial cells filling the septa and compressing the testis tubules. These large eosinophilic clear cells of indefinite outline showed small oval nuclei. No mitotic figures were seen in our specimens. The diagnosis would be difficult from frozen section. Both patients after radical orchiectomy are well over 1½ years. The radical gland dissection did no harm but possibly was not indicated. The radiosensitivity of this tumor has not been studied.

One of the common testicular tumors, the seminoma of Chevassu, is histologically identical to the seminoma or dysgerminoma of the ovary. It is also very similar to a tumor of the pineal body. It probably is of germ cell origin. The seminoma, dysgerminoma, spermatocytoma, or whatever name we may wish to call it, deserves special consideration because it behaves as a clinical entity, having the features of relatively slow growth, delayed metastasis, remarkable radiosensitivity and warrants a good prognosis. Its radiosensitivity simulates the lymphoma. The seminoma is a rounded or lobulated, solid grayish-white *tumor which tends to compress, displace, but rarely to invade, the seminiferous*

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This tumor can frequently be recognized on the microscopic slide with- f the microscope by its lobulation, its dark blue basophilic staining ty. It is composed of large clear polyhedral cells with small but darkly ng nuclei laid down in sheets or strands, occasionally presenting a suggestion cinar formation. Mitoses average 2 to 3 per high power field. Any similar nor with more evident mitosis is considered an atypical seminoma. Serial tions of the entire tumor might disclose embryonal tumor elements and we ust consider this possibility. Hemorrhage into or around these tumors is ex- edingly rare but tendency to spontaneous necrosis is common. The lymphoid ells seen along the fibrous septa adjacent to blood vessels in a certain percentage of seminomata are not regarded as part of the tumor. There is little difference in behavior, radiosensitivity or prognosis of seminoma with or without lymphoid stroma. That is not the differentiating factor between seminoma and the so-called embryonal carcinoma. After the tumors have been entirely destroyed by x-rays in dosage of only 600–800 r delivered in 6 to 7 days, the small areas of dead cells in areas of spontaneous necrosis remain to establish the tentative diagnosis. Seminoma occurred in 109 or 43 per cent of our cases. Metastasis was demonstrated on admission in 15 per cent, retroperitoneal metastatic nodes were removed in an additional 10 per cent. Late metastasis occurred in an additional 4 per cent following surgery.

Seminoma is the common tumor of the atrophic or maldeveloped testis. Twelve of the 13 tumors in cryptorchids were seminomas. The 3 tumors occurring in patients with mumps atrophy and the 5 found in patients with traumatic or idiopathic atrophy were seminomas. At this point we might add that the incidence of testis tumors in soldiers during World War II was approximately 1 per 10,000 troops. By calculation, if we accept the incidence of cryptorchism in adults after Campbell as 0.23 per cent, the incidence of testis tumor in undescended testes is 22 per 10,000, occurring 22 times as commonly as seen in normally descended testes. Our experience paralleled Gilbert's finding that neither orchiopexy nor spontaneous descent have any lessening influence on the development of tumor in a cryptorchid.

The large group of testis tumors which fall into the general category of teratoma testis, presents a difficult pathological picture for interpretation. Ewing's concept of a totipotent cell capable of producing undifferentiated tumors, tumors of one or more primitive germ layer, tumors of immature or embryonic, mature or adult structure demands our serious consideration, for one cannot conceive of various teratomatous elements of the tumor metastasizing to distant parts as a tumor embolus. Such a migration would be expected to produce infarction and this has not been noted. In certain cases the most malignant cells of a mixed tumor may metastasize, leaving behind the less invasive structures.

Classification of testis tumors according to their morphological pattern, undifferentiated carcinoma, adenocarcinoma, papillary carcinoma and teratocarcinoma may enable the pathologist to sort out his specimens but gives the clinician little aid in selection of a plan of therapy nor in prognosis. A division of this group of tumors into embryonal carcinoma and teratocarcinoma results in some benefit to the surgeon but there is no generally accepted concept as to what these terms imply. To one group of workers embryonal carcinoma implies any